THERAPEUTICS IN INTERNAL MEDICINE

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Edited by

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PREFACE

In the past 15 years remarkable progress has been made in the diagnosis and treatment of medical diseases New knowledge has been gained as a result of intensive laboratory research clinical investigation

ment of disease has become so complex that no one individual can claim intimate knowledge of all forms of therapy In compiling this volume on therapeutics it was felt that the book would attain its maximal value to students and practicing physicians if the subject matter were written by a group of outstanding men whose investigations and teaching experience in certain phases of internal medicine qualify them to make authoritative statements Such a group of contributors has written this book and whenever possible, individual preferences regarding therapy have been stressed but not to the exclusion of other commonly accepted practices

The basic plan of the book is to include material related only to the treatment of medical diseases. Since many texts are available giving detailed information regarding etiology and clinical descriptions no general attempt has been made to include such material in this volume However, in certain sections, physiologic principles, classifications of disease, and etiologic factors have had to be correlated with treatment in order to cover the subject adequately Conditions which are

countered by the internist are presented

The editor gratefully acknowledges the co-operation of the contributors in preparing the material for this book The stimulating advice of Dr Frederick Christopher, the technical help of Mrs Jessie O Connell and the suggestions of the publishers have all been of invaluable aid

The editor sincerely hopes that this book will be of value in the dissemination of knowledge regarding the prevention and treatment of medical diseases

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THERAPEUTICS IN INTERNAL MEDICINE

CHAPTER I

THE INFECTIOUS DISEASES

DISEASES DUE TO VIRUSES

COMMON COLD

A specific etiologic agent either bacterial or viral, has not been identified with the disease entity known as the common cold The highly contagious infections involving the upper respiratory tract are usually classified as "colds" This is in contrast to the infections of the lower respiratory system (influenza, "grippe," etc), in which more severe systemic symptoms occur There are no specific therapeutic agents in the treatment of the common cold Efforts, therefore should be directed to the early relief of the symptoms of rhinitis, hoarseness, headache, and aching and to the prevention of serious complications It is also of utmost importance to prevent spread of the disease to other individuals

General Management Bed rest for 24 to 48 hours is the most essential factor in treatment This should not be rigid but vary with the individual case Bathroom privileges are permitted Diet and fluid intake require consideration but rarely offer a problem The diet should be suited to the individual's desire and should be preferably soft. Soft cooked eggs, cereal, milk, eggnog, and fruit

water, milk, tea, and soups should total 3000 cc. This is easily accomplished by the taking of a glass of liquid every hour Purgatives, such as castor oil or magnesium sulfate and enemas, are to be avoided but if constipation becomes distressing a mild laxative (milk of magnesia, 15 to 30 cc, or mineral oil 30 cc) will suffice Some patients are benefited by profuse sweating which may be accomplished by the ingestion of hot drinks, with or without whiskey, or Dover's powder, 5 grains (0 36 mg) every 4 hours for three or four doses High temperatures if present, are best controlled by the use of aspirin, 10 or 15 grains (0 6 or 1 0 gm) The generalized aching and headache are also relieved by a similar dose of aspirin but occasionally it is necessary to prescribe codeine phosphate ¼ or ½ grain (15 or 30 mg) for relief Sore throat may be alleviated by the use of a warm saline or soda gargle (½ teaspoonful of sodium chloride or sodium bicarbonate to a glass of warm water) The use of throat swabs with 10 per cent argyrol, tr of iodine or tr of merthiolate, is to be avoided Chest pain and discomfort may require the use of a mustard poultice applied to the site of distress for 15 or 20 minutes during which time the skin will flush Poultices are not frequently prescribed for as much relief may be obtained by the use of aspirin, grains 10 (0 6 gm) or codeine grain ½ (30 mg)

Relief from Cough The most annoying symptom of the common cold is cough It appears best to suppress rather than obliterate the cough and the drug of choice to meet this end is codeine in dosage great enough to offer relief Usually ¼ or ½ grain (15 or 30 mg) every 4 to 6 hours is sufficient The use of expectorants alone or in combination with codeine has been practiced for years Their effect is usually uncertain The most widely used and probably the most effective of the expectorants is ammonium chloride, 0 3 gm to the dose, given every 3 hours Other expectorants frequently used are as follows potassium iodide 0 3 gm, sodium iodide 0 3

irritative, excessive, or associated with dysp-

nea the use of an opiate is indicated The most widely used opiates are codeine, 1/8 to ½ grain (2 5 to 30 0 mg), dilaudid 1/64 grain (1 0 mg) pantapon 1/12 grain (5 0 mg), and morphine ⅛ or ⅙ grain (8 0 or 10 mg) Except for codeine, the opiates are rarely indicated and in children are contraindicated Distressing intractable cough is only occasionally seen during the common cold but should it occur and fail to respond to codeine, hycodan bitartrate (Endo) 1/12 grain (5 0 mg) may be useful The following cough prescriptions have been used for years and are usually efficient

LOOSE COUGH WITH EXPECTORATION

Ammonium chloride 5 to 8 grains (0 3 to 0 5 gm) to dose

		gm or cc
Ammonium chloride	dr iv	16 0
Syr of citric acid	fl oz	30 0
Water to make	fl oz	120 0

Sig 1 teaspoonful every 3 hours

DRY, IRRITATIVE COUGH WITHOUT EXPECTORATION

		gm or cc
Potassium citrate	dr iv	16 0
Camphorated tr *opium*	*fl oz i*	30 0
Syr of wild cherry	fl oz ii	60 0
Water to make	fl oz iv	120 Mix

Sig 1 teaspoonful every 3 hours

USEFUL CODEINE MIXTURES

		gm or cc
(1) Codeine phosphate	gr viiss	0 5
Ammonium chloride	dr iv	16 0
Syr of citric acid	fl oz i	30 0
Water to make	fl oz iv	120 0

Sig 1 teaspoonful every 3 to 4 hours

		gm or cc
(2) Codeine phosphate	gr iv	0 25
Elixir terpin hydrate to make	fl oz iv	120
Mix		

Sig 1 teaspoonful every 3 hours

		gm or cc
(3) *Codeine phosphate*	*gr iv*	0 25
Syr sedulon (Hoffmann LaRoche) to make	fl oz iv	120 0
Mix		

Sig 1 teaspoonful every 3 hours

OPIATE COUGH MIXTURES

		gm or cc
(1) Dilaudid	gr ss	0 03
Syr of cocoa	fl oz iv	120 0

Sig 1 teaspoonful every 3 hours

		gm or cc
(2) Pantapon	gr iss	0 09
Syr of cocoa	fl oz iii	90 0

Sig 1 teaspoonful every 3 *hours*

COUGH MIXTURE FOR CHILDREN

		gm or cc
(1) Syr of ipecac	fl dr i	4 0
Syr of orange	fl oz ii	60 0

Sig 1 teaspoonful every 3 hours

		gm or cc
(2) Syr of hydriodic acid		
Syr of wild cherry	aa fl oz i	30 0

Sig 1 teaspoonful every 3 hours

		gm or cc
(3) Calcidrine syrup (Abbott)	fl oz ii	60 0

Sig 1 teaspoonful every 3 or 4 hours

It is well to remember that the use of steam, plain or medicated, will control a distressing cough when cough mixtures fail Many types of vaporizers are available To produce a moist, aromatic, medicated steam one may use tincture of benzoin (1 teaspoonful to 1 quart of boiling water), menthol (10 drops of a 10 per cent alcoholic solution to 1 pint of hot water), or oil of eucalyptus (½ teaspoonful to 1 pint of boiling water)

Relief from Nasal Obstruction Therapeutic agents used locally offer the patient temporary relief and the most efficient are the vasoconstrictor drugs Nose drops of ephedrine sulfate, 0 5 to 1 0 per cent solution, neo synephrine (Stearns), 0 25 per cent solution, privine hydrochloride (Ciba), 0 25 per cent solution, and tuamine sulfate (Lilly), 2 per cent solution, are of considerable value in eliminating the nasal congestion Oily suspensions placed in the nose are contraindicated, particularly in the very young and the aged because of the danger of lipoid pneumonia The benzedrine sulfate (S K F) inhaler and tuamine sulfate (Lilly) inhaler are helpful and obviate the instillation of a liquid into the nose It is well not to give benzedrine sulfate or neo synephrine to the hypertensive individual or one with cardiac disease Atropine sulfate, 1/150 to 1/100 grain, will quickly control the rhinorrhea but its unpleasant side effects makes its use undesirable Nasal tampons of 10 or 20 per cent argyrol (Barnes) and/or 0 5 or 1 per cent ephedrine sulfate are valu

able in the later stages of the disease when the nasal secretions become thick tenacious and difficult to dislodge

Use of Sulfonamides and Antibiotics The routine use of the sulfonamides penicillin aureomycin and other antibiotics is rarely indicated and should be reserved for the individual showing signs of secondary bacterial invasion or lower respiratory tract involvement Their use will be described under complications of the common cold In fact, the promiscuous routine use of these drugs should be discouraged for they fail to alter the clinical course and in addition they carry with them some danger of toxic reactions and the possibility of producing an allergic state

Use of the Antihistaminic Drugs The antihistaminic drugs have gained some popularity particularly among the laity as an aid in aborting the common cold Results are dubious Pyribenzamine benadryl neoantergan thephorin and histadyl are a few of the many antihistaminic drugs available The prescribed dose varies from 25 or 50 mg three or four times a day given at the onset of the cold and continued for 2 days These drugs may be of value in those individuals with an allergic rhinitis or in those allergic individuals whose symptoms are accentuated by the upper respiratory infection The side reactions associated with their use such as sleepiness vertigo weakness drowsiness cerebral stimulation insomnia and tremors make their use limited Individuals operating machines or vehicles engaged in dangerous occupations or responsible for the safety of others should avoid the use of these drugs

Treatment of Complications Sinusitis The sinuses may become involved during an attack of the common cold by secondary bacterial invasion or by the result of inadequate drainage If drainage is adequate acute sinusitis will usually subside spontaneously and treatment is directed to relief of local symptoms and to the control of the infectious process Bed rest in a warm moist room for the duration of the acute process is necessary Steam plain or medicated is valuable in humidifying the room The facial or frontal pain may be relieved by aspirin 10 or 15 grains (0 6 or 1 gm) codeine ¼ or ½ grain (15 or 30 mg) and/or heat moist or dry applied over the involved sinuses To promote drainage vasoconstrictor nose drops sprays or tampons (1 per cent ephedrine sulfate 0 25 per cent neosynephrine hydrochloride 1 0 per cent privine hydrochloride and 1 0 per cent tuamine sulfate) are beneficial Slight negative suction will further promote drainage The response in many patients to penicillin treatment is most dramatic Aqueous procaine penicillin 300 000 or 400 000 units given intramuscularly every 24 hours will often abort the condition prevent further spread of the infection and markedly reduce the need for surgical intervention Aqueous penicillin 50 000 units every 3 hours is also effective Penicillin is also beneficial when administered by aerosol or in dust form 50 000 units of penicillin per cubic centimeter administered four or five times a day is a valuable form of treatment The Vaponefrin Company supplies an atomizer which delivers a fine spray of penicillin and offers a suitable and simple method of disseminating penicillin to the sinuses Abbott Laboratories also supply a simple portable plastic aerohalor for nasal and oral inhalation which dispenses 100 000 units of penicillin dust Dosage varies from 100 000 to 300 000 units a day In resistant cases rather than attempt further medical care consultation with an otolaryngologist should be obtained

Otitis Media Not infrequently the individual with the common cold develops otitis media Most of the infections are the result of pneumococcal and streptococcal invasion of the middle ear and are amenable to penicillin and sulfonamide treatment Intramuscular aqueous procaine penicillin 300 000 or 400 000 units every 24 hours and intramuscular aqueous penicillin 50 000 units every 3 hours are specifics Equally beneficial although on rare occasions producing severe drug reactions is sulfadiazine 0 5 or 1 0 gm every 4 hours with an equal amount of sodium bicarbonate Heat by means of a heat pad or a well covered hot water bottle to the ear aids in relieving pain Analgesic ear drops are important in the early stages of the otitis media Three to 5 drops of auralgan (Doho) or 1 per cent phenol in glycerin dropped in the ear every 2 or 3 hours will relieve pain Fortunately penicillin and the sulfonamides usually prevent an increase in the amount of pus but if bulging occurs

paracentesis under local or general anesthesia becomes necessary Any further spread of infection with the development of mastoiditis or lateral sinus thrombosis demands specialized surgical intervention

LARYNGITIS When laryngitis develops the management as described for the common cold should be rigidly continued The patient is instructed to rest not to speak or whisper Smoking is prohibited It is advisable to avoid atropine and opiates of all forms for they decrease secretion which is desired Penicillin aureomycin and the sulfonamides are of no value No local treatment is necessary

BRONCHITIS This is one of the more frequent complications of the common cold Fatigue exposure chilling and allergy seem to predispose to its development The patient must remain in bed until the temperature has been normal for at least 2 days Smoking should be avoided Fluids to 3000 cc a day are continued as during the period of the acute cold Steam inhalation is of utmost benefit Symptomatic relief of headache is accomplished by prescribing codeine ¼ or ½ grain (15 or 30 mg) or empirin compound with codeine ¼ grain or aspirin 10 or 15 grains (0 6 or 1 0 gm) every 4 hours Penicillin is the antibiotic of choice if a pneumococcus or streptococcus is the secondary invader administered in doses of 300 000 or 400 000 units of aqueous procaine penicillin once or twice a day depending on the severity of the infection Aqueous penicillin 50 000 units every 3 hours is also used In many patients no specific organism is isolated In such cases aureomycin is more desirable than penicillin Its recommended dose is 1 gm four times a day until symptoms regress then 250 mg four times a day Reduction in the dose of aureomycin often becomes necessary because of the nausea vomiting or diarrhea it may induce

Vaccines Mixed bacterial vaccines given orally or parenterally have been disappointing in their result and their use is not to be encouraged

Vitamins Polyvitamins or specific vitamins offer no specific prevention Their value is limited to individuals who develop protracted colds and show signs of nutritional deficiencies

Sulfonamides and Antibiotics These agents have been tried as preventives for the common cold but results are extremely disappointing Sulfadiazine has had clinical trials and will not affect the course of the common cold and should be restricted to specific complications The same holds true for mass prophylaxis with penicillin

Prevention Isolation of the patient and avoidance of contact is essential in preventing the spread of the common cold Control of atmosphere ultraviolet irradiation dust control measures and the use of glycol vapors have been shown to be effective in reducing the spread and incidence of respiratory diseases The disinfection of air by these means necessitates specialized equipment which may in the future be utilized in the construction of buildings and hospitals

RENO ROSI

INFLUENZA

Recent advances in viral studies have shown the specificity of influenza and one must consider the term as applied solely to the *disease produced by influenza viruses* types A and B It is characterized clinically by severe constitutional symptoms of fever chills headache prostration muscular aching and cough Symptoms and severity vary with each particular outbreak

Prevention With the increasing knowledge of the cause and spread of influenza there have been added impetus and advancement in the attempt to control and eventually to eradicate the disease

Experimental and clinical evidence has shown that the virus of influenza is primarily air borne With this evidence there have been attempts to control the atmosphere by means of chemicals (glycol vapors) or ultraviolet irradiation Methods of utilizing these agents are still experimental equipment is complicated and now rests in the hands of architects working with clinicians designing buildings and hospitals for the future

Immunization against Influenza Two methods of immunization have been employed namely producing active immunity with influenza vaccine and supplying passive immunity by serum The latter has shown to be of no value in preventive therapy Somordintseff et al have reported excellent

protection in man by the intranasal spraying with high titered immune sera prepared from horses This has not been corroborated by other investigators

In contrast to the use of serum the subcutaneous injection of influenza types A and B vaccine has been shown to be effective in producing active immunity It appears that vaccination will probably be valuable in preventing epidemics if an adequate potent vaccine is available and is given to large enough numbers of people Studies carried out under the control of the Commission on Influenza of the United States Army Epidemiological Board showed that vaccination produced a protective effect of short duration The vaccine used by this group consisted of a suspension of formalin inactivated influenza viruses of representative strains of types A and B A single injection of 1 cc was given subcutaneously In 1943 44 12 500 ASTP students were studied in each study alternate individuals receiving virus vaccine the others a control injection Results showed that 7 1 per cent of the unvaccinated and 2 2 per cent of the vaccinated groups were hospitalized for influenza Other studies have substantiated these findings The success of influenza vaccine rests on the premise that the disease must involve an etiologic strain or strains which is similar to the strain or strains contained in the vaccine

Influenza virus vaccine containing both types A and B viruses is prepared from allantoic fluid of chick embryos injected with various strains of influenza virus types A and B Inactivation is produced by formalin

DOSAGE The recommended dose for adults is one injection of 1 0 cc subcutaneously and for children two 0 5 cc injections 7 days apart The duration of immunity following this dose is not known and if unusual epidemic conditions prevail it seems a good policy to repeat a dose of 0 5 cc A booster injection is advisable 6 to 12 months after the basic immunization The unfavorable results to influenza vaccine are those of local soreness erythema and systemic manifestations of chills fever and muscular aching

In unusual instances fatal anaphylactic shock has been reported In persons known to be sensitive to eggs or chicken feathers it is wise to proceed with caution and a preliminary skin test dose of 0 01 cc. of the undiluted vaccine should be given

INDICATIONS FOR VACCINATION Vaccination of whole populations against influenza seems inadvisable It is better to concentrate on those who are susceptible to protracted respiratory infections and on those groups in which one desires to reduce time loss from their work. In the latter group students industrial workers hospital personnel and the military are particularly important to immunize

Active Treatment No specific treatment is available Bed rest and the judicious use of chemotherapeutic agents and antibiotics are necessary Bed rest is imperative and should be continued throughout the febrile period and the first 3 to 4 days of convalescence The diet should be varied to suit the individual s desire preferably liquid to soft The fluids ingested should total 3000 to 4000 cc a day In general the management of the patient with the common cold pertains to influenza Acetylsalicylic acid 5 or 10 grains (0 3 to 0 6 gm) empirin compound with codeine ¼ grain and codeine ¼ or ½ grain (15 to 30 mg) will usually relieve the generalized aching and headache A warm humid atmosphere is desirable

The sulfonamides penicillin and aureomycin are frequently prescribed since influenza predisposes to invasion of the respiratory tract by secondary organisms such as streptococci pneumococci, and staphylococci They have no specific action on the influenza virus but have a decided effect on the secondary invaders In most cases they are not used unless complicating signs appear Sulfadiazine 15 grains (1 0 gm) with an equal amount of soda bicarbonate every 4 hours sulfonamide mixtures (sulfathiazole sulfadiazine sulfamerazine) (1 0 gm) every 4 hours are frequently used Penicillin is also effective in controlling complications when administered intramuscularly in aqueous solution 50 000 units every 3 hours or as aqueous procaine penicillin 300 000 or 400 000 units daily Aureomycin has been used with some apparent benefit in atypical pneumonia and although its use in influenza has not been established, it holds promise The recommended oral dose has not been determined but 1 0 gm four

tımes a day untıl symptoms regress followed by 500 mg four tımes a day seems to be adequate

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PSITTACOSIS

Psıttacosıs an elementary body dısease caused by the vıral agent Mıyagawanella ıs

lovebırds have contrıbuted to ıts spread Furthermore overwhelmıng evıdence has established the fact that pıgeons sea gulls doves *ducks and chickens are infected* and contrıbute to human ıllness Petrels on the Faroe Islands and ın Iceland are reservoırs of the vırus Human psıttacosıs has repeatedly been traced to canarıes and some finches The dısease sometımes erupts ın house epıdemıcs and study of some of these has revealed *many of its characteristics* (Meyer Meyer and Eddıe)

In recordıng the hıstory of a patıent under observatıon for possıble psıttacosıs ınfectıon ıt ıs ımportant to note whether or not he has had contact however slıght wıth the bırds or mammals whıch may be reservoırs As ın all heterogenous ınfectıon chaıns the element of chance here plays a role and fleetıng exposure sometımes escapes notıce The dıagnostıcıan must constantly bear ın mınd that despıte the desıgnatıon of psıttacosıs" or the ımplıcatıon of the term "parrot dısease" any specıes of bırd partıcularly those enjoyed by fancıers must be suspected as a source of pneumonıtıs

Preventıon GENERAL MEASURES The deep seated love for bırds and ın some ınstances theır economıc value make *it useless* to preach as a paramount prophylactıc measure that parakeets lovebırds pıgeons chıckens ducks and other bırds be excluded from human dwellıngs and theır surround

to create and to maıntaın a bırd ındustry free from psıttacosıs Theır efforts have been thwarted because the majorıty of owners and breeders cannot be convınced that the dısease exısts and ıs of real danger to human beıngs and they do not follow ınstructıons or obey the sımple rules of preventıon Consequently, health officers of many states and Unıted States terrıtorıes found ıt necessary wıth the rısıng ıncıdence of the dısease *to request modification* of the Interstate Quarantıne Regulatıons the recommended laws became effectıve ın June 1947 They specıfy that no person shall offer psıttacıne bırds for transportatıon or *transport such* bırds ın ınterstate traffic unless owners accompany the shıpment, and the shıpment must not exceed 2 bırds No sanıtatıon program has to reduce rısks from or ducks

ACTIVE IMMUNIZATION Since Rivers and Schwentker in 1934 actively immunized several laboratory workers with living virus the possible danger of creating the carrier state by this method has been recognized and it has never been used even to protect laboratory workers or bird dealers Lately phenol killed ether extracted yolk sac suspensions of virus elementary bodies have been employed in several laboratories for the protection of personnel (Wagner et al) but the value of these protective inoculations has not been determined

PROPHYLACTIC MEASURES AGAINST HUMAN TO HUMAN INFECTION The infectivity of the psittacosis virus is well known Human to human infections have been observed and proved In at least 23 instances involving 30 nurses the disease developed after exposure to infected persons and contact with diseased birds was definitely excluded Of particular interest is the fact that nurses or attendants may become infected and in turn may transmit virus to others In the experiences of Eaton Beck and Pearson the infection spread from one man to 3 nurses In the 1943 epidemic of severe pneumonitis in the Bayou region of Louisiana the death of 8 nursing attendants exposed to a patient 48 hours before death and the illness of 11 others emphasize the importance of direct contact in human to human transmission (Olson and Treuting) Statistics such as these should serve to remind physicians that the occupational hazard to themselves and to nurses is considerable The instances described and others of the past indicate that the sputum of human beings may harbor the agent of psittacosis No definite rules can be given as to the period of quarantine In any event it is imperative that disinfection and disposal of buccal discharges be carefully supervised For their protection nurses should wear rubber gloves and cellophane masks The virus resists desiccation and is readily dispersed in the air in droplets projectile coughing heavily contaminates the environment Patients should be confined in isolation rooms having minimal air currents and protective measures designed to prevent escape of air into wards and halls of the hospital The experiences reported by Loizaga and Auerbach in a hospital in Buenos Aires attest to the risks involved when patients with unrecognized psittacosis are cared for in open wards

Treatment TREATMENT OF THE ATTACK In principle symptomatic treatment and nursing should follow procedures now used in typhoid The convalescent patient should be carefully watched in the majority of cases resolution is slow and relapses have been observed

SYMPTOMATIC TREATMENT Proper nourishment is quite important and frequent small feedings are indicated Fluids should be given freely and in adults the intake should be kept at 3000 to 4000 cc per day Tepid sponge baths to reduce temperature are always indicated Efforts should be made to improve the patient s well being An ice cap may make him more comfortable and sometimes is efficacious in decreasing fever The delirious patient of course requires particular attention since in his delirium he may get out of bed and injure himself Insomnia may be treated with 0 1 gm of seconal To relieve the constipation which is sometimes troublesome mineral oil or citrate of magnesia may be used although soapsuds enemas are recommended Codeine (30 mg) is the most useful drug for treating headache Cough is rarely of importance expectorant drugs should be administered only when a specimen of sputum is desired for laboratory diagnosis

CONVALESCENT SERUM TREATMENT Between 1930 and 1944 treatment with conva [illegible]

dose was from 50 to [illegible]00 cc and was administered intramuscularly or intravenously From the limited reports available it is difficult to judge objectively the value of this therapy

CHEMOTHERAPY As early as 1930 Brink [illegible]

plied supportive evidence of its efficacy after tests in mice Their observations have not since been further confirmed nor has the drug been employed in any large series of human infections More recently (1948) Hurst demonstrated that "nitroakridin 3582" (Hochst) or 2, 3-dimethoxy-6-nitro 9 (3 diethylamino-2 hydroxypropyl) amino-acri

dinedihydrochloride possesses moderate therapeutic activity against the viral agent of psittacosis in mice

Sulfonamides Early experiments by Rudd and Burnet and unpublished observations of Eddie and Meyer offered no proof that any of the sulfonamide compounds is of any value against the majority of known strains of the *psittacosis virus* With the strains of virus at the disposal of Hurst, sulfadiazine and sulfamezathine constantly failed to prevent death in mice and usually prolonged but slightly the mean period of survival Bieling and Heinlein claimed that sulfanilyl urea was curative in some experiments Meiklejohn et al and Early and Morgan found sulfadiazine effective against two classical psittacosis strains (6BC and Gleason) These observations may in part explain the clinical cure reported by Hinshaw In view of the greater effectiveness of penicillin on all strains thus far tested, there is no need to resort to sulfonamide therapy in psittacosis

PENICILLIN Heilman and Herrell Bedson and May, Meiklejohn et al, Wiseman et al, and Early and Morgan studied the effect of penicillin on experimental psittacosis in the mouse and found it to be highly favorable Workers at the Hooper Foundation (Meyer, Eddie, and Quan), treating experimentally infected mice and ricebirds obtained convincing therapeutic results when treatment was instituted early in the course of the infection, and the antibiotic was used in large doses Ricebirds often relapsed and died 22 to 27 days after discontinuation of intensive treatment (6 000 000 units over a period of 17 days) Penicillin has also been found to have a definite effect on the course of the disease induced in chick embryos by the viruses of psittacosis and of meningopneumonitis (Parker and Diefendorf) To maintain comparable concentrations in man, however, would require the daily injection of millions of units of penicillin In view of these experimental studies, it was argued that penicillin in all probability would be ineffective in therapy of human psittacosis Using the chick embryo testing technic, Eaton et al experimented with the murine, feline, and meningopneumonitis viruses and likewise concluded that these agents were relatively insusceptible to penicillin The favorable clinical results reported, on the other hand, have invalidated the early conclusions Turgasen was the first to report on the apparently favorable effect of penicillin in a case of psittacosis Treatment was instituted on the eighth day of illness and consisted of injection of 100 000 units per day On the third day the temperature was normal A similar result was noted by Flippin, Gaydosh, and Fittipoldi, although penicillin therapy was not instituted until the 19th day of illness Parker reported recovery of patients 61 and 52 years of age, respectively, whose psitta [illegible] fifth and seventh hospital days, respectively The temperature of one patient dropped from 104 5° to 98 6° F on the second day of the penicillin treatment, but continued to fluctuate for several days between 98 6° and 101 4° F A normal temperature was reached by lysis on the 11th hospital day (15th day of the illness) in a second case Recovery followed promptly after institution of penicillin therapy on the 10th day of illness with 520 000 units in the case reported by Kirkwood In the laboratory infection described by Rosebury and collaborators the dramatic resolution of symptoms followed combined therapy with penicillin and sulfadiazine which was begun on the fourth day of the illness The strain of the psittacosis virus which caused the infection responded favorably to either therapeutic agent Rosebury et al expressed the view that the combined therapy and the patient's previous vaccination were responsible for the good results

Through the courtesies of the attending physicians, Meyer and Eddie (unpublished observations) had occasion to review over a period of 3 years the histories of 68 psittacosis patients who had received penicillin in the course of their treatment The clinical diagnosis had been confirmed through serologic tests or isolations of the virus or both conducted in the laboratories of the Hooper Foundation Most of the patients had received sulfonamides before penicillin was administered Of the patients treated at different stages of the disease 4 or 5 per cent died, apparently as a result of inadequate therapy or undetermined complications Whenever penicillin was given in large doses improvement was usually prompt and even

dramatic in several cases In 6 laboratory infections proved to be psittacosis through isolation of virus from the sputum or blood or both the patients received penicillin as the sole therapeutic agent The victims of the infection belonged to the age group of 25 to 55 The antibiotic was given parenterally in daily doses of from 80 000 to 320 000 units total doses ranged from 980 000 to 3 190 000 units over a period of 10 days The following observations are significant

In one case of viremia in which the psittacosis agent was demonstrable in the sputum the condition responded promptly to a relatively small dose of from 80 000 to 160 000 units daily for 10 days a total of 1 470 000 units although recovery was slow Consequently in a later case with similar manifestations the dose was increased to 40 000 units every 3 hours or 320 000 units daily Before treatment the course was toxic with marked malaise severe headache and remittent fever (with swings from 99 8° to [illegible]

[illegible] matic and clinical improvement began 48 hours after initiation of specific treatment the patient was afebrile on and after the [illegible]

[illegible] days

These observations pointed the way for subsequent treatment schedules in psittacosis Daily doses of not less than 300 000 units and a total dose of from 2 600 000 to 3,200 000 units over a period of about 10 days are now employed Large initial doses (up to 100 000 units every 4 hours) are particularly recommended if diagnosis has been delayed and [illegible]

[illegible] essential it is not surprising to record that crystalline penicillin G proved ineffective in the treatment of 3 human infections while aureomycin established cures Studies on the dynamics of penicillin suggest that this antibiotic acts on the extracellular phase of the viral agent when it is not actually multiplying Whenever the immunity mechanism is sluggish or impaired by toxins penicillin treatment must be prolonged until the antibodies of the host are capable of taking over the bacteriostatic and bactericidal effects of the antibiotic How far the multiplication within the host cells may be inhibited by penicillin is not known Experiments on mice and the observations on one human psittacosis virus carrier failed to furnish much encouragement Over 10 000 000 units administered parenterally or by inhalation exerted no effect on the localized respiratory infection of the human carrier The virus was again isolated from the sputum several weeks after treatment had been discontinued Early and intensive treatment of the infections reduces the number of viral elements and permits the normal body defense mechanism to dispose of the few stragglers The serum of several patients treated with penicillin was again examined 6 to 12 months after the first studies and invariably the complement fixation titer had dropped to 1 2 or 1 4 This in the light of previous experience rather definitely indicates complete autosterilization and freedom from viral elements

The introduction of penicillin has enriched the therapy of psittacosis Adherence to the suggestions outlined will reduce the number of carriers prevent the development of the carrier state and diminish the unduly high human fatality rate (20 per cent)

It is not unlikely that aureomycin (or duomycin) may replace penicillin Preliminary trials with 5 to 20 mg per kilogram of body weight have yielded encouraging results in infected mice and birds Daily doses for intramuscular injection should range from 0 5 to 1 0 gm The drug may also be given orally in doses of 2 to 4 gm daily *

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* The importance of aureomycin and chloromycetin as possible potent therapeutic agents in psittacosis cannot be overemphasized Woodward has recently pointed out the effectiveness of both antibiotics in patients infected with the agents of psittacosis and lymphogranuloma venereum Herrell has also indicated the usefulness of aureomycin in psittacosis —*Editor*

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HERPES ZOSTER

Herpes zoster is an acute virus infection of the dorsal root ganglia or extramedullary ganglia of the cranial nerves with secondary involvement of the skin Typically, the clinical picture is ushered in with the sudden appearance of tense vesicles surrounded by a zone of erythema, along the skin segment supplied with sensory nerves of the ganglion or ganglia involved The pain is intense, burning, constant, and radiates along the affected root It is resistant to treatment and may last weeks to years Hyperesthesia of the involved skin segment is usually present Motor weakness may be associated with the sensory change Herpes of the opthalmic division of the trigeminal nerve may be serious because of ocular complication Central nervous system involvement has been reported and spinal fluid examination in these patients reveals a pleocytosis

Local Treatment Local treatment is directed primarily to protecting the lesions from infection and trauma and to the relief of pain and itching Ordinary dusting powders of equal parts of zinc stearate, starch and talc, or of thymol iodide, are applied three times a day to the involved areas which are then covered with thick pads of

absorbent cotton If the vesicles are unruptured collodion may be painted over the affected site Carbolized calomine lotion (1 per cent phenol) in generous application three or four times a day is helpful for its soothing effect Seventy per cent alcohol applied locally and covered with abundant loose cotton batting will protect the hyperesthetic areas When irritation of the skin develops wet dressings of Burows solution (1 10) are of value

The number of therapeutic agents recommended for relief of pain of herpes zoster is an indication of the lack of specificity of any one of these agents Deep roentgen therapy directed over the involved ganglia 200 to 300r daily for 4 to 6 days is frequently successful Spraying of the involved skin with ethyl chloride gives temporary relief but has not been effective in producing complete relief In the more severe cases paravertebral block gives excellent results Ten cubic centimeters of 0 5 or 1 0 per cent procaine solution is injected with a No 22 spinal needle

through an area of infected vesicles This treatment is of great value in the hands of those competent enough to perform this type of block When carried out within the first 72 hours of the infection results are excellent The longer the disease has progressed before injection the less striking is the result In older individuals paravertebral block does not afford as much pain relief Thiamine hydrochloride 100 mg injected into and beneath the area of eruption has been advocated but results are inadequate

Relief of Pain by Drugs In many patients local treatment fails to relieve the persistent agonizing pain of herpes zoster and analgesic drugs and opiates must be used Sodium salicylate 15 or 20 grains (1 0 or 1 3 gm) four times a day or 2 tablets of empirin compound four times a day will lessen the pain When these fail one may resort to codeine ½ to 1 grain (15 to 60 mg) every 4 hours Morphine sulfate ⅙ grain dilaudid 1/32 grain and demerol hydrochloride 50 or 100 mg are used only in rare cases of prolonged and unbearable pain Pituitrin 0 5 or 1 0 cc intramuscularly every 24 hours for 3 or 4 days is also used Its use is contraindicated in pregnancy hypertension and cardiac disease A striking relief from pain is often obtained by the daily intravenous injection of 1 or 2 gm of sodium iodide given during the acute phase of the disease until the pain subsides The danger

50 or 100 mg of thiamine Diphtheria antitoxin 5000 units intramuscularly has been used but there is little justification for its administration The possibility of anaphylaxis and serum reaction in sensitive individuals makes its administration dangerous* Benadryl 25 or 50 mg four times a day for 5 or 6 days affords some patients relief but results are inconsistent The same results are obtained with other antihistaminic drugs such as pyribenzamine neoantergan thephorin and others

Reports on observations of the use of aureomycin in relief of herpes pain have been most encouraging Frequently its action is

hours for 3 or 4 days is adequate Although further studies are necessary early reports indicate that aureomycin may be the drug of choice in this disease The value of chloromycetin is not known

Reno Rosi

MEASLES

Measles is an acute infectious highly communicable disease of universal distribution characterized by prodromal catarrhal symp

agent

Prophylaxis Public health measures for the control of measles are generally ineffective Any susceptible individual who is exposed to the disease is likely to develop it It is highly contagious in the prodromal period which accounts to a great extent for the rapidity of its spread The contagion is lessened after the rash has reached its peak Most health departments require isolation for a period of 7 to 10 days after onset of the rash Children under the age of 10 years who have had direct contact should be placed

under quarantine for a period of 14 days from the day of exposure Adults are not restricted in their activity

There are now specifics available which are effective in preventing or modifying measles in contacts In general, it is preferable to modify rather than prevent, in order that the individual may develop his own active immunity and thus be rendered immune to future exposures Under certain conditions, however, prevention is best, these include (1) children under 3 years of age, an age group in which the mortality is highest, (2) children who have other acute or chronic disease (3) children in hospital wards, and (4) susceptible women in the first trimester of pregnancy

Convalescent serum, immune gamma globulin, placental extract, and adult human serum are effective in preventing or modifying measles Of these convalescent serum and immune gamma globulin have gained the greatest favor These agents if used for prevention produce a transient passive immunity, lasting up to a month, and will prevent measles only within that period Convalescent serum is available at serum centers located in large urban areas No standard dose is recommended but in general 10 to 20 cc given intramuscularly during the first 3 days following exposure will afford protection The same amount given on the fourth to the eighth day after contact usually gives a modifying effect After the eighth day the effect diminishes and is practically nil after the 11th day Reactions are rarely seen Although an effective agent in preventing and modifying measles, the use of convalescent serum is limited because of its relative scarce supply

Since World War II, immune gamma globulin processed from pooled normal human plasma has been available and is more extensively used because it is more easily obtained than convalescent serum Clinical trial has shown it to be as effective as any other protective or modifying agent Immune gamma globulin is prepared so that each 1 0 cc contains 160 mg of gamma globulin It is concentrated to a titer 25 times greater than in normal human plasma For modification 3 0 to 3 7 mg of gamma globulin per pound of body weight should be administered intramuscularly during the first 6 days of the incubation period The dose of immune gamma globulin varies, depending on the effect desired, namely, prevention or modification, the age and weight of the person, and the day of the incubation period The following intramuscular dose schedule is recommended for modification by the Cutter Laboratories

Weight (lbs)	*Total Dosage (cc)*
15	0 3 to 0 4
20	0 4 to 0 5
25	0 5 to 0 6
30	0 6 to 0 7
35	0 7 to 0 8
40	0 8 to 0 9
45	0 9 to 1 0
50	1 0 to 1 2

For complete protection five times as much should be given early in the incubation period (15 mg or more of gamma globulin per pound of body weight)

Studies by Bundesen showed that there was little difference in results obtained by various prophylactic agents given before the fifth or sixth day Top and Badger, however revealed a marked improvement in results in giving injections during the first 3 days of the incubation period

With the easy availability of immune gamma globulin, the need for adult human serum and placental extract has practically disappeared Larger doses of adult serum are necessary, varying from 10 to 80 cc intramuscularly Intramuscular placental extract is usually administered in 2 to 10 cc doses for prevention and 2 5 cc for modification Local and systemic reactions of mild to moderate severity may occur

It is well to remember that the diagnosis of modified measles may be difficult for there is a marked amelioration of signs and symptoms The incubation period may be prolonged, the rash may be minimal, and the fever low grade or absent

Active Treatment The treatment of measles is symptomatic and no specific antibiotic or chemotherapeutic agent has been developed to reduce further the present low death rate The patient should be isolated in a warm room Rest in bed during the acute febrile period is imperative The diet should be adequate, preferably liquid or soft

[illegible]

warm boric acid solution [illegible] also aid in relieving conjunctival irritation In patients with distressing symptoms resulting from upper respiratory involvement (laryngitis, tracheitis, bronchitis) relative high room temperatures and increase of humidity are a help Steam inhalation, plain or medicated with menthol or tr of benzoin reduces the severity of cough For the younger children a croup tent is a great help Cough mixtures containing small amounts of codeine (⅛ to ¼ grain) (8 to 15 mg) to suppress the cough should be given Suitable preparations are

		gm or cc
Codeine phosphate	*gr iii*	*0 18*
Elixir terpin hydrate	fl oz iv	120 0

Sig 1 teaspoonful every 3 hours for cough

		gm or cc
Codeine phosphate	gr iv	0 24
Syr wild cherry	fl oz iv	120 0

Sig 1 teaspoonful every 3 or 4 hours for cough

Aspirin, 5 to 10 grains (0 3 to 0 6 gm), or aminopyrine, 5 grains (0 3 gm.) three or four *times a day, is effective in reducing* high temperatures Fevers not reduced by these antipyretics may be controlled by tepid water sponging or alcohol rubs Sulfonamides and antibiotics are reserved for those cases in which complicating secondary infection occurs and the agent used depends on the invading organism Sulfadiazine, 5 to 15 grains (0 3 to 1 0 gm), with an equal amount of sodium bicarbonate, every 4 hours, aqueous procaine penicillin, 400 000 units intra [illegible]

[illegible]

supportive measures and oxygen Once the disease has manifested itself, intramuscular or intravenous convalescent serum appears to be of little *or no value* The use of large doses, 500 cc or more, in the pre-eruptive stage has held some promise, but the cost, the difficulty in obtaining such large amounts of serum, plus the uncertainty of results, *make its use unfeasible*

Frequent examination of the ears is essential If otitis media has developed aqueous penicillin, 50,000 units intramuscularly every 3 hours, aqueous procaine penicillin, 300,000 *or 400,000 units every 24 hours, or sulfadia*zine, 5 to 15 grains (0 3 to 1 0 gm.) every 4 hours, is indicated and is usually effective If ear pain is severe and the tympanic membrane is bulging, paracentesis may be necessary *Frequent examination of the mastoid* in these patients is important

The nose should be kept clean and comfortable Vasoconstrictor drugs (0 5 to 1 0 per cent aqueous ephedrine sulfate, 0 25 per *cent neosynephrine (S K F) solution) will frequently give relief from nasal obstruction* Oily suspensions are contraindicated Zinc oxide ointment or petrolatum applied to the [illegible]

mands diligent supportive care Oxygen by nasal catheter or tent is of great help Convalescent serum, although of questionable *value, should be administered, 100 to 300 cc.* intravenously Mild sedation is important, phenobarbital, ⅛ to ½ grain (7 5 to 30 mg), chloral hydrate, 5 or 10 grains (0 3 to 0 6 gm), and sodium bromide, 15 grains (1 0 gm), may be used to control irritability, delirium marked restlessness, and convulsions Maintenance of the patient s nutrition [illegible]

gavage mixture may be made up of milk, [illegible]

venous infusion of 5 or 10 per cent glucose in distilled water or normal saline, may be given to maintain adequate fluid intake at 3000 cc a day *In those patients showing* shock, infusion of 500 cc. of normal human plasma may help In selected cases transfusion of 300 to 500 cc. of whole blood to adults and 200 to 300 cc to children may be necessary If urinary *retention occurs cathe*terization is necessary

Reno Rosi

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RUBELLA
(German Measles)

Rubella is a mild acute highly communicable disease resembling measles and scarlet fever The etiologic agent is probably a *filtrable virus although it has never been* isolated Characteristic occipital posterior auricular and posterior cervical adenopathy occurs

Treatment Rubella is so mild that no *treatment other than symptomatic measures* is indicated Bed rest is advisable during the *febrile period which rarely lasts for more* than 2 or 3 days Fever is readily combated *by acetylsalicylic acid 5 or 10 grains* (0 3 or 0 6 gm) three times a day A liberal *fluid intake (3000 cc a day) is advised* The diet should be soft The enlarged lymph nodes are *rarely painful but should* pain develop the application of cold compresses gives relief

Prevention Reports have suggested that a relationship exists between the occurrence of rubella in the first trimester of pregnancy and congenital anomalies such as cataracts congenital heart disease deaf mutism and mental deficiency Further statistical study regarding this relationship is essential With this possible danger confronting the mother it appears that some means should be carried out to prevent her from contracting the disease Immune gamma globulin should be given to all pregnant women exposed to the disease in spite of the fact that its efficacy has not been determined The dose of gamma globulin has not been established but it should be large *10 to 15 cc* intramuscularly if early in the incubation period and 15 to 20 cc if late Some physicians have advised therapeutic abortion for those women who contract rubella in the early *months of pregnancy*, but there is no agreement among the profession on this radical procedure It is felt that the final decision on this phase of management must await further observation and the possibility of other factors in producing these deformities It follows that the female patient who develops rubella early in life may be considered fortunate Certainly young female children should not be given immune gamma globulin for prevention of rubella

Isolation is carried out during the acute phase of the disease and the patient is excluded from activity for 7 days Contacts are not quarantined

RENO ROSI

MUMPS

Mumps is an acute infectious disease of man caused by a specific virus and characterized by swelling of one or more of the salivary glands usually *the parotids A decided tendency to* involve the testes ovaries mammary *glands central nervous system and pancreas* is noted Its occurrence is universal and it is *more prevalent during the winter and spring* months Its highest incidence is in the age *group of 5 to 15 years but many adults contract* the disease, particularly those crowded *in schools camps barracks ships etc*

Treatment Bed rest with bathroom privileges *for the febrile period and until disappearance* of salivary gland swelling is the most important factor in the *treatment of* mumps If the gland is extremely tender *cold compresses* may afford relief *In patients* with high fever nausea and vomiting *fluids* should be administered *parenterally*

intake by mouth should reach 2500 to 3000 cc a day *Solid food should be avoided* during the period of acute salivary gland swelling because of the pain *encountered* in chewing The liberal use of acetylsalicylic acid *5 or 10 grains (0 3 or 0 6 gm)* or of empirin compound with codeine ½ grain *(15 mg), is useful in relieving pain* and aching Seconal 1½ grains (0 1 gm), phenobarbital *1 grain (60 mg), and nembutal* 1½ grains (0 1 gm), are useful in relieving *restlessness and promoting sleep* Atropine sulfate is of no value About 1 per cent of

patients develop a painless presternal edema for which no treatment is necessary

ORCHITIS Bed rest is considered to be important in the prevention of orchitis but there is not general agreement on this procedure In young patients orchitis is uncommon and this may indicate that the inactive testis is resistant to infection with mumps virus On this theory diethylstibesterol which inhibits testicular function is prescribed Prophylactically 2 mg of diethylstilbesterol are given every morning Therapeutically, diethylstibesterol is valuable in reducing the severity and the duration of the acute orchitis The dose is 5 mg given orally each morning until the orchitis subsides Local treatment consists of (1) proper support usually by means of an adhesive bridge which relieves the discomfort produced by the weight of the enlarged inflamed testes (2) local application of an ice bag (3) acetylsalicylic acid 5 or 10 grains (0 3 or 0 6 gm) every 4 hours or codeine ¼ or ½ grain (15 or 30 mg) Surgical treatment of mumps orchitis is generally not necessary but some physicians feel it is indicated for those patients with an enlarged hard painful testicle and persistent chills and fever The procedure advocated is an incision through the tunica vaginalis and multiple incisions of the tunica albuginea The release of fluid by incision brings about relief of pain and usually lowers the temperature The procedure necessitates gas anesthesia Surgical intervention appears to be too radical and is not indicated in mild or moderate cases or in patients with a predominant epididymitis The use of convalescent serum to prevent orchitis has a sound immunologic basis but is not practical The dose is usually 40 to 50 cc given intravenously Pooled normal plasma 100 to 200 cc intravenously has little effect in reducing the incidence of orchitis Gellis gave 20 cc of gamma globulin prepared from mumps convalescent serum and reported excellent results Gamma globulin prepared from normal plasma has no effect

MENINGO-ENCEPHALITIS The symptoms of meningeal irritation severe headache stiff neck, nausea and vomiting, associated with an increase of lymphocytes in the spinal fluid is not uncommon in mumps The prognosis is good Lumbar puncture is performed to establish the diagnosis and usually the amount of fluid removed is sufficient to relieve the severe headache Multiple or daily spinal punctures are not advisable for the symptoms subside spontaneously or with the use of acetylsalicylic acid 10 or 15 grains (0 9 or 1 0 gm) or codeine ¼ grain (15 mg) given four times a day

PANCREATITIS This complication is occasionally seen and is characterized by severe upper abdominal pain nausea vomiting and abdominal distention Signs of ileus may be present The serum amylase is markedly elevated Treatment is conservative and it is imperative to recognize the condition as an acute nonsurgical condition of the abdomen During the acute phase nothing is given by mouth and parenteral fluids (5 or 10 per cent glucose in normal saline and protein hydrolysate totaling 3000 cc a day) are given to maintain fluid balance Codeine ½ grain (30 mg) morphine sulfate ⅙ grain (10 mg) or demerol hydrochloride 50 to 100 mg will usually relieve the abdominal pain

MASTITIS This condition may occur in either sex but is uncommon It requires no treatment other than the application of cold compresses to relieve the pain and swelling

OOPHORITIS Oophoritis is much less frequent in females than orchitis is in males It is essential to differentiate this condition from surgical abdominal lesions particularly acute appendicitis Treatment is conservative Cold compresses applied to the involved side and the use of liberal amounts of aspirin will control the pain

Prevention No practical method of active immunization is available in preventing mumps The disease acquired before puberty is mild and mass prophylaxis is of little value Convalescent serum 50 to 100 cc intravenously early in the incubation period will afford passive immunity and is recommended for adults who have been exposed and for seriously ill and debilitated children Unfortunately mumps convalescent serum is expensive and difficult to obtain Gamma globulin is of no value Stokes and his coworkers presented evidence that increased resistance could be produced in many children who received 1 0 cc of formolized mumps virus subcutaneously The formolized vaccine had no effect when given during the incubation period of the disease

Quarantine of the patient until the swelling of the salivary glands has subsided is advised No restrictions are placed on adult contacts

RENO ROSI

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CHICKENPOX
(Varicella)

Chickenpox is a universal benign acute infectious highly communicable disease caused by a filtrable virus and characterized by mild systemic symptoms and a typical rash When secondary infection of the skin eruption develops it may be difficult to differentiate from the pustular stage of small pox

Active Treatment Symptomatic treatment is the rule and efforts are directed to prevention of secondary infection In most cases particularly children the disease is so mild it requires no treatment Bed rest is advised during the febrile period Fever is combated by the use of aspirin 5 or 10 grains (0 3 or 0 6 gm) given every 4 hours *The diet should be soft or light with ample* quantities of liquids 2500 to 3000 cc a day *The itching is controlled by soothing lotions* such as carbolized calomine lotion applied liberally to the skin twice a day If a generalized pustular eruption occurs it is well to cleanse the skin with boric acid solution three or four times a day and apply wet dressings of potassium permanganate solution 1 5000 or Burow s solution 1 8 When crust formation has occurred 5 per cent sulfathiazole or sulfadiazine ointment may be applied Careful attention to the hands and fingernails is important The hands should be washed carefully with soap and water and the fingernails cut short to prevent scratching *In patients who are distressed* unduly by the itching phenobarbital ⅛ or ¼ grain (7 5 or 15 mg) four times a day should be prescribed

The sulfonamides and antibiotics have no effect on the course of the disease but should be used if secondary infection of the skin occurs *Sulfadiazine* 7 5 or 15 grains (0 5 to 1 0 gm) with equal amounts of sodium bicarbonate *may be employed* but its use has decreased considerably because of the specificity of penicillin Intramuscular aqueous procaine penicillin 300 000 or 400 000 units once or twice a day controls the majority of secondary infections

Central nervous system complications (meningitis meningo encephalitis) are extremely rare and the prognosis is excellent *Headache is usually the only distressing* symptom and is controlled by aspirin 5 or 10 grains (0 3 or 0 6 gm), every 3 or 4 hours When convulsions and restlessness occur phenobarbital ¼ or ½ grain (15 or 30 mg) chloral hydrate 10 grains (0 6 gm) three or four times a day should be prescribed

Prevention Chickenpox is so mild in young children that no attempt is made to prevent the disease Quarantine of the patient until the primary crusts have disappeared is essential The prophylactic use of 2 to 6 cc of gamma globulin given intramuscularly during the incubation period or after exposure has been disappointing Vaccination of individuals with vesicular fluid is not advised The use of convalescent serum 15 or 20 cc intravenously, may aid in preventing or modifying the disease and should be administered to seriously ill or markedly debilitated children It is not generally available

RENO ROSI

SMALLPOX
(Variola)

Preventive Treatment *Smallpox* vaccination in infancy with revaccination every 5 to 7 years and promptly before or after probable exposure have greatly decreased smallpox morbidity and mortality

ISOLATION OF PATIENT Whenever possible the patient should be promptly transferred to the nearest isolation hospital where smallpox is treated A special ambulance is desirable the person transferring the patient should be vaccinated with potent vaccine

before he comes in contact with the patient. The physician should have been recently vaccinated and should wear rubber gloves or use an aseptic hand technic to prevent the spread of the virus to susceptibles

Specific Treatment The only specific treatment is prophylaxis by vaccination Sulfonamides and penicillin are of value only in the prevention and treatment of the usual secondary streptococcal and staphylococcal infections

General Treatment Good nursing care is of paramount importance Sedation should be adequate to ease pain and lessen discomfort At first, sponge baths twice daily with tepid water or aqueous zephiran chlo-

worst areas should be sprayed with aqueous zephiran chloride solution (1 1000) or repeatedly with a penicillin solution (10 000 units per cubic centimeter) Sulfathiazole as a dusting powder or ointment is applied to the most infected areas The mouth is irrigated after each meal with tepid soda solution (1 teaspoon per 1000 cc)

The eyes require gentle, repeated care Excess of pus is carefully wiped away with sterile gauze or cotton soaked with warm saturated boric acid solution Then ophthalmic sulfathiazole, penicillin, or borated ointment is applied to the margin of each lid These nursing measures are repeated six or more times both day and night The ears and genital organs are treated in the same way if lesions there cause much discomfort A glass drinking tube, rubber bulb, and drinking cup (with spout) are invaluable aids The diet should include ample fluids and vitamins, 100 mg of ascorbic acid daily is of value Only when extensive and painful lesions in the mouth and throat prevent swallowing of adequate food and fluids should intravenous fluids and medication be used They are otherwise contraindicated on account of the risk of blood stream infection When the odor is especially repulsive, wet dressings of potassium permanganate solution (1 10 000) are applied and changed every 4 hours Premature removal of scabs makes pitting more likely A penicillin tablet (50 000 units) given by mouth every 3 hours

well tolerated and is safer than the muscular route

Varioloid This modified form of smallpox occurs in patients who have been vaccinated earlier in life and who have since lost most of their immunity The eruption usually appears after a 2 day prodromal period, the pustules are superficial and the lesions seldom terminate in scarring The treatment is as outlined, but less frequently applied

LOUIS W SAUER

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SMALLPOX VACCINATION

(Vacc n a)

Procedure Primary vaccination * is best administered to infants or young children during the first spring or autumn after completion of the other customary immunization procedures The most approved technic both for primary vaccination and revaccination is the multiple pressure method because it is painless and highly successful A secondary infection and disfiguring scar are far less likely to occur† The preferred site is the upper left arm at the depression caused by the deltoid insertion The skin is cleansed with soap and water or wiped with a sterile swab of acetone or 70 per cent ethyl alcohol After the skin is completely dry, the entire contents of one capillary is deposited at the site

fingers above The lower surface of the arm is

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* Only fresh

† A scar results from secondary infection, it is erroneous to assume it implies immunity

held firmly with the left hand so that the skin at the vaccination site is stretched slightly This facilitates penetration of the virus into the deeper layers *where it then multiplies* The side of the needle point held at a sharp angle (almost parallel to the surface) is pressed firmly and rapidly with a perpendicular motion into the drop of vaccine—10 times in as many seconds for primary vaccination 20 to 30 times for revaccinations Only ⅛ sq in should be involved The site is then promptly but gently rubbed with the side of the needle tip to impregnate the virus further *before the left hand is released* Excess of vaccine is wiped off with sterile cotton If the inoculated area is kept limited *the lesion and scar remain small Trauma of* the skin should be avoided blood should not appear The site need not be covered Scratching might transfer virus to another surface and produce more lesions If a sterile gauze dressing is applied to protect against scratching it should be loose and is to be removed the following day When the vaccination "takes" a shield should never be worn because the vesicle dries more rapidly *with ventilation Perspiration under a shield* increases itching and a secondary infection is likely to result The vesicle which usually appears between the third and 10th days is proof that a take" has occurred

Treatment of Lesion During the first 10 days of a primary take" the area should be kept dry Water should not touch the skin there because maceration of the vesicular surface may rupture the lesion permitting secondary invaders *to gain entrance Oozing* of the contents should be avoided as it in*creases the likelihood of secondary infection*

swelling and inflammation many physicians advise frequent dusting of the area with powdered boric acid (from a sifter top can) six to eight times daily An accelerated reaction a small *vesicle within 2 days after*

pustule formation A traumatic reaction resulting from cross scratching or scarification may simulate an immune reaction Use of impotent ("dead") vaccine may lead to a fals interpretation of immunity

If it is desirable to protect the vesicle fo *a few days* a sterile gauze pad (3 by in) should be held in place with a narrov strip of adhesive across the top only (like a apron) This may be raised each time befor the powdered boric acid is applied the gauz should never adhere to the scab

Revaccination A previously vaccinate person may be immune without the presenc of a visible scar Many fatal cases of small pox have resulted from the erroneous as sumption that the patient was immune wher a revaccination did not take" because a inert ("dead) vaccine was used Revaccina*tion may be performed at any time of th* year and should be repeated every 5 to 7 years If a prompt take or evidence of im munity is desirable two vaccinations about 1 in apart may be performed on both arms The preferred site for revaccination is just above the old scar if a scar is not found the vaccination should be repeated at the del toid insertion of the left arm The presence of keloid tissue in the vaccination scar usually *disappears in the course of several years*

Complications Secondary infection of the vaccination lesion is usually pyogenic As a rule it responds to such simple measures as keeping the area dry with liberal repeated applications of powdered boric acid Penicillin solution (10 000 units per cubic centi meter) may be sprayed from a nebulizer eight or more times daily If improvement is not prompt penicillin by mouth (50 000 *units) every 3 hours for 3 days* or a daily intramuscular dose (300 000 units) for 2 or *3 days is beneficial Secondary infection* occasionally is due to tetanus The familiar clinical symptoms such as trismus and convulsions should be recognized early Previous routine immunization with tetanus toxoid (as in DTP) protects against this complication Generalized vaccinia is likewise infrequent When it is extensive penicillin should be used both locally and internally Post vaccinal encephalitis is rarely encountered in this country It is more likely to occur in individuals with central nervous system instability

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RABIES

Rabies is an acute infectious disease of lower animals caused by a neurotropic filtrable virus The virus is transmitted either from animal to animal or from animal to man by the introduction of infected saliva through the broken skin or intact mucous membrane The disease is invariably fatal to man and to practically all warm blooded animals

The treatment of rabies is so far entirely prophylactic No patient known to have acquired the disease has survived The elimination of the disease among animals and adequate prophylactic treatment in man must be our aim if we are to conquer the rabies problem

Prevention of Rabies in Animals REGULATION IN ENGLAND The British Isles is an outstanding example of a country in which rabies in animals has been prevented and regulated Years ago it was recognized that the dog reservoir was the only important source of rabies in England The care of dogs was regulated It was required that animals be kept on their owners premises or that they be effectively restrained by leash and/or muzzle when they were taken off the premises Restrictions were placed on the shipping of dogs from one area to another and all dogs imported into the country were quarantined in isolation at the port of entry for 6 months in order to be sure that they were not in the incubation period of rabies By these simple and sensible means the disease was completely eliminated and did not reappear in England until World War I when the import regulations program was relaxed and a few dogs were flown in from the Continent

It would seem the best way to eliminate rabies in the United States would be to follow the practice of those countries which have successfully controlled the problem

IMMUNIZATION OF ANIMALS In addition to the regulation and care of animals, there is now available a means of actively immunizing an animal against the disease However more than a single dose of vaccine should be required for vaccination It is difficult to justify the belief that a single dose of rabies vaccine given once a year to the average dog will produce solid immunity when it is common knowledge that we must give a human being 14 to 21 doses of vaccine to prevent the disease The contribution of such men as Webster and Casals of the Rockefeller Institute and of Habel of the United States Public Health Service would indicate that single dose vaccinations are at best only partially effective Much of the vaccine that was used until recent years was demonstrated by Webster and Casals to be entirely without antigenic properties Apparently the newer ultraviolet treated vaccines have greater antigenic value Some veterinarians have insisted that at least three doses be given in series to produce adequate immunization and this viewpoint seems justified

There is however no test known to demonstrate that any given animal is actually immune Immunization carries with it the danger of false security Many people who have had their dogs vaccinated will thereafter fail to co-operate in the continuation of the care that should be exercised until rabies has been completely eradicated Only constant education of the public will emphasize the ever present danger of rabies even in a well cared for dog

PREVENTIVE MEASURES FOLLOWING INJURY Following an injury by an animal certain procedures should be complied with The word injury is used advisedly since bites are not the only important type of injury Dogs cats and other animals lick their paws and a rabid animal is most likely to be salivated which means that the claws may be contaminated with saliva It is therefore unimportant whether a human injury has resulted from an animal bite or is the result of clawing by an animal

The name address and the age of the injured person, the site and the time of the injury and a description or identification of the offending animal should be immediately reported to the police or health department

pound, completely isolated from all other animals For legal reasons, it should be kept within the health jurisdiction in which the injury occurred The animal should be care fully observed for a period of 14 days, if there is any sign of rabies this should be reported The animal should be allowed to die from the disease, and the head should be carefully removed by a veterinarian, packed in ice and immediately transported to a re liable laboratory A brain if not properly cared for, will deteriorate so markedly that a reliable examination for Negri bodies becomes impossible after a few hours

In the laboratories of the Illinois State Health Department, it is customary to examine for Negri bodies at once and to do mouse inoculations on all cases where there is a question of human contact This procedure verifies the microscopic diagnosis and, according to authoritative work it will pick up about 10 per cent more cases of rabies than can be found microscopically

If the animal cannot be identified or ap prehended, the injured person must be treated as though the animal had been rabid In the case of injury about the head and neck, the antirabic treatment should be begun without delay If the animal is not immediately found and the injury is about the trunk or extremities a 3 or 4 day delay is warranted until a concerted effort in lo cating the animal can be made

Treatment of Wounds The use of fum ing nitric acid or phenol on wounds is still widely recommended, but the work of Shaughnessy and Zichis indicates that a 20 per cent solution of soft soap used to wash thoroughly and to irrigate wounds in animals is as effective as any type of chemical cauter ization A lacerated wound should not be closed by suture, in every case of primary suture, experience has taught that the re opening of the wound has been necessary because of infection

The probability of acquiring rabies as the result of an injury from an offending rabid animal varies considerably according to the type and location of the wound Babes of the Pasteur Institute has undoubtedly given the most authentic figures in his Table of Probabilities, he expresses in percentages the likelihood of developing rabies without treatment

Babes' Table of Probabilities

Type and Location of Wound	*Animal*	*Chance of Infection (Percentage)*
Multiple deep—		
eyes, nose, lips	Wolf	100
eyes, nose, lips	Cats	70
eyes, nose, lips	Dog	60
rest of face	Dog	50
rest of bare areas	Dog	30
Single deep—		
fingers neck	Dog	15
Superficial—		
uncovered areas	Dog	10
if bled freely	Dog	2
Infected saliva		
on recent wound		0 1
on 24 hour old wound		0 0

A complete review of statistics on rabies is published in *The Tenth Report on Data of Antirabies Treatments,* compiled by Major Greenwood * and supplied by the Pasteur Institute This includes the final summary of the health section of the League of Nations, and gives statistics on more than 1,250 000 series of treatments

Of the 250,000 people treated during the period covered by this report, the over all mortality rate was 0 21 per cent lower than during any previous period Of the 228 051 people treated there were 41 cases of post vaccinal paralyses with only 8 deaths The total of 10 reviews of the League revealed that, of the 1 290,758 cases treated, there

accidents from the use of vaccine

If these figures are compared with the percentage calculations in Babes' Table of Probabilities, it is obvious that the chance of any kind of postvaccinal paralysis is only one eighth as likely as the chance of acquir ing rabies from contamination of a fresh wound by saliva The chance of dying of a postvaccinal accident is only ¼th as great as the chance of acquiring rabies from wound

* Bull Health Organization League of Nations 11 12 301, 1945-46

contamination It is difficult to reconcile these facts with the reticence some physicians show in the use of rabies vaccines Physicians who do not hesitate to recommend a cholecystectomy in spite of known definite mortality may quiver at the thought of giving a series of rabies vaccine This statement is not intended to encourage the useless administration of rabies vaccine but to give comfort to the physician who has to give such treatment Hodges reports that the mortality is 30 times as high in untreated injuries from rabid animals as it is with vaccine treatment

Rabies Vaccine The Semple vaccine and the irradiated vaccine which is distributed by the Illinois State Health Department are the types of vaccine which are commonly used and have been proved safer than the older types Following the work of Webster Casals and Habel, the antigenic properties of those now sold and distributed in this country are well established

At the present time standard treatment consists of the subcutaneous injection of from 14 to 21 doses of one of the vaccines The 21 dose treatment is most generally used for severe lacerated wounds from known rabid animals or for wounds about the head and neck Two doses are to be given daily for the first week and one dose per day for the second week these can be usually distributed over the outer sides of the arms and thighs The anterior abdominal wall has been frequently recommended but modern clothing makes this location unsuitable For wounds through clothing over the trunk and lower extremities 14 doses at one day intervals are usually administered

Many physicians feel that fairly large doses of vitamin B complex given during the period of treatment may help to protect against paralytic accidents This idea is not statistically supported at the present time but the use of this relatively harmless addition to treatment is recommended

Several years ago Dr Habel and again at the 1949 Convention of the American Medical Association Dr Koprowski reported on the use of hyperimmune serum concentrates as the most promising development in years for the prophylactic treatment of rabies Dr Koprowski found that a single injection of hyperimmune serum around the area of the injury protected animals against rabies more adequately than 14 doses of vaccine The administration of the vaccine immediately following the use of the serum has not been as effective as delayed treatment Dr Habel feels that the serum should be given immediately after the injury then after a seven day waiting period, seven to 14 doses of vaccine should be administered for late effect As the serum becomes available this should become the treatment of choice

Even in the massive statistics of the League of Nations and the Pasteur Institute it is evident that a delay of 14 days from the time of the injury does not affect the mortality statistics in rabies and that an incubation period of less than 30 days does not allow for protection by rabies vaccine Serum on the other hand has given immediate protection in a high percentage of cases and the reduction in number of necessary vaccine injections will reduce the number of post vaccinal paralyses

Reaction from Rabies Vaccine. The average patient who is given rabies vaccine will experience only mild discomfort this has been the case where more than 200 series of vaccine have been administered. A reaction, which might be described as an Arthus phenomenon occurs in about half the cases The patient experiences no discomfort during the first seven or eight injections but on the eighth or ninth day there will be a red indurated itching area at the site of each previous injection which also appear subsequently at the site of each new injection I have never found it necessary to discontinue treatment because of a reaction I have seen only one case of multiple neuritis with considerable weakness followed by complete recovery of function The literature contains many instances of encephalitis postvaccinal paralysis transverse myelitis and some fatalities

In recent years Dr Sellers of Georgia has reported some fatalities He and many others have emphasized particularly the danger of a repeated series of vaccine in patients who have been frequently exposed they have concluded that fatal accidents do not follow any series of less than seven to 10 injections It would seem rational that an individual who has been previously treated with a full series of [illegible] vaccine will have a sufficient

stimulation of immunity following a booster series of seven doses From the mortality rates, some physicians have concluded that one should never give vaccines *to any per* son who has not actually been bitten by a rabid animal

Cases of exposure without actual injury from the animal are unusual but they do occur It is, therefore, recommended that a careful history and examination should pre cede any opinion as to the advisability of giving vaccine in each individual case

INDICATIONS FOR USE OF RABIES VACCINE AND/OR SERUM *The necessity for giving* rabies vaccine is the most serious decision to be made by the attending physician This may be translated as follows "Is the danger of the patient s contracting rabies from the injury in question greater than the slight risk incurred by the use of vaccine?" In spite of the recognized danger of such a procedure the generally accepted indications for the use of rabies vaccine and the special cases in which there might be some question in the minds of many physicians as to the advisa bility of giving vaccine are listed below

Vaccine should be given if an individual has been injured

(1) by a wolf, fox, coyote, skunk or any wild animal that cannot be apprehended,

(2) by a rabid dog cat, or other domestic animal,

(3) by a dog or cat that cannot be appre hended or identified

(4) by any of the above animals when the offending animal is deliberately killed *less than 10 days after the injury,*

(5) if an individual has been bitten by a healthy animal which becomes rabid within 14 days of the injury

In any case where an animal dies or is killed, the brain should be examined micro scopically and a mouse inoculation should be done If the brain is in such a condition that these procedures cannot be carried out satisfactorily, one must assume that the ani mal *was rabid Opinions may differ in special* cases, but experience and a thorough search of the literature would add the following indications

(1) In the case of an animal injury about the head and neck, antirabic treatment should be given at once unless there has been no rabies within 50 miles during the preceding year The reason for this is natu rally due to the short incubation period in such injuries, unless hyperimmune serum is *available, rabies will not be prevented in the* shortest of these periods, even by immediate treatment Limited quantities of serum are available, as larger quantities become avail able, hyperimmune serum should be given at once and then discontinued for one week If the dog is not rabid at that time, further treatment is unnecessary If the dog has become rabid, a series of rabies vaccine should be given

In one such case in which a 21 dose series was given, the patient became irritable, apprehensive, and feverish on the 10th day His temperature *reached* 103° F by the 11th day and his muscles showed spasmodic twitching The elder Dr Lagorio, who was with the Pasteur Institute in Chicago, ad vised the continuation of the treatment This was done and the patient returned to normal before the last dose was given Dr Lagorio felt that this represented an abortive case of rabies, he believed he had seen such cases twice previously His impression was that the *immunity was just sufficient to tip the* bal ance in favor of the patient My usual prac tice has been to give seven doses of rabies vaccine, beginning immediately following any head or neck injury If the offending animal is well at the end of this time, treat ment is discontinued and the results of observation are awaited

(2) Antirabic treatment should be given to the patient who has been licked on mu *cous membrane surfaces by a rabid* animal, this is particularly true of very young chil dren or infants Virus can penetrate the mu cous membrane, at least one case of death from rabies is known in which the only established contact occurred when the rabid dog licked the vulva of the patient

(3) Rabies vaccine should be given *to any* patient when there is grave suspicion or definite knowledge of contamination of a fresh wound with the saliva of a rabid ani mal This indication requires careful history and examination It is not necessary to give vaccine to everyone who has been in con tact with a rabid animal, and vaccine should rarely be necessary for patients who have not been injured by a rabid animal How *ever, it should be kept in mind* that there

have been cases of definite exposure in the absence of animal injury

TREATMENT OF RABIES After the onset of the disease rabies vaccine is entirely useless in the treatment of human rabies All known cases, up to the present time have resulted fatally The severe convulsive seizures are terrifying and painful Anticonvulsant therapy, which may require large doses of intravenous barbiturates is indicated here the treatment would cease except for the possibility of help from recent developments

One of these might be the use of large quantities of pooled human serum from patients who have been given rabies vaccine within a year Evidence of effectiveness in other virus diseases is not good but if such serum should become available it might be worth trying A procedure similar to that used in a severe case of tetanus by Dr Vernon C Turner and Dr T C Galloway might be applicable here if we find that death in rabies may be due to secondary effects of the virus infection in the brain as Dr Galloway has found to be the case in bulbar poliomyelitis In the case of tetanus referred to curare was used as the anticonvulsant it was given to the point of respiratory paralysis The patient was placed in postural drainage position—25 to 30° elevation of the feet—in a respirator and a tracheotomy was done to enable the maintenance of a clear airway This patient recovered from tetanus If such measures were used we might find that rabies is a self limited disease and that by maintaining life through the acute stage the patient might recover from the infection

Another promise looms large in the newer discoveries in antibiotics Aureomycin and chloromycetin seem to be effective in diseases caused by certain of the larger viruses Since the rabies virus is one of the largest with which we deal it would seem logical that animal trials should be begun at once to determine whether either of these antibiotics is effective in rabies

MARTIN SEIFERT

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ACUTE POLIOMYELITIS

The treatment of poliomyelitis has been the subject of an abundant literature for at

eral, the real contributions of each have been incorporated into our armamentarium and procedures of questionable value have been discarded It is not the purpose of this section to deal with any particular regimen of therapy, but rather to present generally accepted methods of proved efficacy This discussion will be limited to the acute course of the disease and hence will not deal with re habilitation and orthopedic procedures

Until recently the treatment of poliomyelitis was primarily the management and attempted correction of crippling sequelae Our increasing fundamental understanding of the disease process has made it possible to recognize and emphasize the importance of the acute symptoms and findings As a result, abortive and nonparalytic forms of the disease have been recognized with increas ingly greater frequency Further, we have

to clarify some of the baffling epidemiologic aspects of the disease The latter group, having brain stem and cranial nerve nuclear lesions, is of paramount importance from the standpoint of mortality Finally there is some evidence that an awareness and knowledge of early symptomatology leading to early diagnosis and proper expectant management may prevent the evolution of a classical paralytic illness

The clinical diagnosis of poliomyelitis is a presumptive one and is usually made without difficulty It is important, however, that we realize its presumptive nature Spinal fluid and physical findings are frequently

cephalitis, Guillain Barré syndrome, mumps, meningo-encephalitis, cerebrovascular accidents, and peripheral neuritis, must be constantly borne in mind Further, we are forced to admit that there is no way of predicting which patient will experience a mild clinical course with eventual complete functional recovery, or, on the other hand, which individual will have extensive involvement with or without permanent physical handicap In view of this circumstance it behooves us to maintain an attitude of intelligent skepticism in appraising the results for any particular form of therapy

A direct approach to the treatment or prevention of acute poliomyelitis remains as a primary aim of the abundant investigational efforts now being concentrated on this disease At present there is no antibiotic, chemotherapeutic, or biologic agent which is

serum have not been substantiated Our hopes for gamma globulin have been dissipated by such careful studies as that of Bahlke and Perkins Although several theoretical possibilities for antiviral chemotherapeusis have been studied in experimental animals, only one, phenosulfazole (darvisul), has seemed promising enough to warrant a trial in human subjects It was found to be entirely ineffective (Grulee et al) Although antibiotic substances such as sulfadiazine, penicillin, or aureomycin constitute impor tant parts of the therapeutic management of bulbar, bulbospinal, and some spinal types of poliomyelitis, they are used only to control or prevent secondary bacterial infections and are not antiviral It follows then that the treatment of poliomyelitis is indirect Our efforts are directed toward counteracting the effects of the pathologic process by sympto matic therapy, physical means, and general supportive procedures

Isolation Procedures It has been stated that the occurrence of paralytic poliomyelitis is a coincidence in the process of mass exposure Expressed in a different manner, at least during periods of high case incidence, the virus of poliomyelitis is so widespread that acquisition of the infection is more a function of individual susceptibility than of specific exposure In the past, extreme isola-

tion precautions were practiced, based on ignorance and dread of the disease more than on specific knowledge of the manner of its spread The presence of the virus has been demonstrated in the nasopharynx for periods of up to 8 days after the onset of symptoms (Howe et al) The spread of virus from this source must be entertained as a possibility Further the presence of virus in the stools of convalescent patients for periods of 4 to 6 weeks is well established Theoretically then it should be our purpose to protect against the possibility of respiratory spread during the first days of the clinical course and thereafter against enteric spread In the former connection the use of face masks is far from ideal and in fact is

sterilization of feces is most difficult to accomplish by practical hospital methods Finally, if proper sewage disposal is available the danger from fecal contamination is negligible It is then recommended that dejecta *be carefully handled and promptly disposed* of into hopper or toilet without attempted sterilization

Although health department regulations in some localities demand 3 weeks, 2 weeks is the most common requirement for isolation and recently a period of one week is *being recommended* as adequate It is common practice to employ gown and mask technic with enteric precautions for 2 weeks though not attempting the sterilization of dejecta The hands are carefully washed with soap and running water both before and after an isolated patient has been examined or, in the case of a poliomyelitis unit or ward upon entering and leaving the isolated area

Prophylactic Measures The physician is often called on to give advice concerning the avoidance of *infection As has been inferred* previously, there are no specific biologic chemotherapeutic, or antibiotic substances available for this purpose However, there are several general recommendations that can be made In the majority of instances attempting to run away from poliomyelitis accomplishes little but to upset the normal pattern of living and thereby to increase the physical stresses to which children particularly are exposed Further, the possibility *of encountering the disease* in the new environment is a real one At times when poliomyelitis is epidemic, no illness however minor, should be neglected The ailing individual should be put to bed and the advice of a physician solicited All reasonable measures of personal hygiene should be emphasized *in the home and elsewhere Every effort* should be made to maintain regular daily habits of living avoiding physical, dietary and other excesses or indiscretions It is reasonable to wash all uncooked foods and to boil drinking water for at least 5 minutes if there is a question of contaminated supply In the latter connection it is pertinent to recall that no epidemic of poliomyelitis has been known to have been water borne Finally the suggestion is frequently offered that unnecessary exposure to crowds should be avoided This should not be construed however, to mean that such regulated public gatherings as schools and theaters should be categorically advised against Actually the relative risk of school exposure is probably much less than that incurred during the uncontrolled *play activities of children On the* other hand, the opening of a rural school during a local epidemic of poliomyelitis could afford a common exposure of geographically isolated individuals in which case it should remain closed temporarily The question of whether public and semiprivate swimming pools should continue to function during epidemics is a difficult one If superchlorination of the water is accomplished and further if excessive fatigue and chilling are not incident to use of the pool its continued operation is acceptable though not necessarily desirable

Psychologic Considerations The impact of acute poliomyelitis upon patients their families and communities can be devastating In considerable part this unfortunate *reaction can be prevented* In the first place physicians must assume responsibility in fostering public education concerning the disease In addition, they must help to outline a positive program for their *community* and to denounce firmly the imposition of ridiculous and unjustifiable measures stemming from and in themselves contributing to public hysteria A few minutes spent describing the disease, explaining the condition of the

patient and answering the questions posed

ner The family can be cautioned against the overt display of their apprehension in the patients presence and as a consequence of these changes in familial attitude most effective reassurance can be furnished the patient Among professional personnel an attitude of confidence friendliness and businesslike but unfrenzied performance of all necessary procedures cannot be overemphasized Finally by the intelligent use of diversional therapy such as reading music games and other forms of simple entertainment depressing introspection and loneliness can be minimized

Fluids and Diet The usual acute clinical course of poliomyelitis does not exceed 7 to 9 days Unless there is respiratory dysfunc

adequate to furnish the optimal daily requirements are desirable as in any well conceived dietary Certainly vitamin or caloric deprivation is not justified as a therapeutic measure with the possible exception of the patient remaining relatively immobilized for long periods by reason of quadriplegic involvement or need of artificial respiration In these cases moderate restriction of milk and the withholding of supplementary vitamin D are justified because of the danger of renal calculus formation

Parenteral alimentation is resorted to when danger of respiratory obstruction exists as is the case when diaphragmatic or intercostal musculature is paralyzed and lesions of the glossopharyngeal or vagus nuclei result in swallowing difficulty or again in the bulbar patient when damage to the cardiorespiratory centers in the dorsal reticular formation of the medulla gives rise to irregular shallow respirations with variable periods of apnea If the patient requires artificial respiration and is enclosed in a cabinet type of respirator intravenous subcutaneous or rectally administered fluids can nevertheless be given without appreciable difficulty by utilizing the small stoppered port in the roof of the respirator A fitted cork penetrated by a short section of sterile glass tubing is attached to the infusion equipment In general terms the quantity of fluid administered varies from approximately 50 cc per kilogram of body weight per day in the adult to 125 cc per kilogram per day in very young children Of this total calculated amount not more than one third is allowed to be salt-containing Obviously under circumstances of excessive sweating or repeated vomiting such a rough rule as the above does not apply and one must be guided by careful clinical appraisal and the determination of blood electrolytes Five per cent glucose in sterile distilled water which is isotonic with the blood plasma serves adequately to make up the remainder of the daily fluid requirement In those instances in which technical difficulties preclude the possibility of the intravenous administration of fluid hypodermoclysis and proctoclysis can be utilized to great advantage

Before leaving the subject of parenteral fluid administration mention should be made of the use for specific therapeutic purposes of two intravenous solutions namely hypertonic glucose and hypertonic saline with repeated lumbar drainage of cerebrospinal fluid The hypothesis that hypertonic glucose solutions favorably affect the inflammatory process within the central nervous system is supported only by the clinical impressions of a few observers The second therapeutic approach listed above has been generally abandoned as ineffective and as not without

Gavage feedings constitute a most useful and convenient method of providing nutriment to selected patients with impairment of pharyngeal or respiratory function However in either type of case it must be initiated with the greatest care and only after progression of the clinical findings has ceased for at least 24 hours If this precaution is not observed there is great risk of crucial difficulty with excessive mucus stimulated by the introduction of the tube Such an occurrence in a critically ill patient with the resultant hypoxic episode can be and not infrequently is fatal A thorough trial of 5 per cent glucose or normal saline precedes the administration of milk amino acid prep-

arations or high caloric fluids by this route In our experience the use of a polyethylene tube approximately 1/16 in diameter is ideal for gavage purposes Through it a constant drip can be maintained with the rate of flow so adjusted as to prevent overfilling of the stomach Any one of several high caloric feedings of known composition is suitable

Elimination Constipation is an early and common complaint in acute poliomyelitis and may persist for as long as 2½ weeks In the majority of instances this difficulty is thought to be due to temporary derangement of the motor innervation of the bowel but of course there are also patients in whom paralysis of abdominal and diaphragmatic musculature is a contributing factor Frequently a warm saline enema every second or third day is all that is required Mineral oil by mouth or occasionally as a small retention enema at night is helpful and rarely is the digital disruption of a fecal impaction required Strong cathartics and saline purges should be avoided Fortunately the patient may be assured of complete return of proper bowel function

Urinary dysfunction during the acute *course of this disease is considerably less* frequent than constipation but may be quite severe disturbing to the patient and troublesome to manage All degrees of urinary dysfunction may be encountered from slight *difficulty in initiating micturition to com*plete retention Since the duration of even severe manifestations is rarely more than a few days serious complicating infection can usually be avoided by intelligent management The presence of urinary dysfunction in small children and infants may be missed since attendants interpret overflow dribbling as the normally frequent urination of this age group The simple expedient of inspecting the lower abdomen for fullness in the midline and palpation with percussion of vesical dullness will reveal the true state of affairs The trial of such maneuvers as attempted micturition in the sitting position pouring warm water over the perineum and hot sitz baths are helpful in mild cases and should be tried Occasionally a patient will be able to void if allowed to recline in a bath tub of warm water A next logical step is the use of parasympathomimetic drugs *The most useful of these* described by Lawson and Garvey in 1947 is furfuryl trimethyl ammonium iodide or furmethide It is given orally in doses varying from 1.25 to 7.5 mg Unfortunate side reactions are not frequent and since the drug is rapidly dissipated the dosage may be repeated after 30 to 45 minutes In a small percentage of patients catheterization must be resorted to Since the expected duration of urinary dysfunction is short the bladder is emptied on one or two occasions by simple catheterizations before

gram for a child or 3 to 5 gm per day for an adult Rarely is an indwelling catheter essential In addition to the danger of detrusor paralysis in the male some authors state that urinary dysfunction is prolonged if this expedient is resorted to (Horstmann)

Physiotherapy In a disease which is associated with paralytic manifestations as well as variable degrees of tightness or spasm of the muscles of the body a respect for body mechanics and the intelligent application of

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second the prevention of early deformities and the overstretching of muscles third the promotion of optimal nutrition of muscle tissue which has temporarily at least been deprived of normal innervation Finally but not of least importance is the use of positioning as a part of general therapy for the patient Reference is made here particularly to the dependent drainage of secretions from the oropharynx and tracheobronchial tree in the prevention of both respiratory obstruction and hypostatic pneumonia

All gradients of postural drainage can be employed from elevation of the foot of the bed on 10 to 12 in shock blocks to short intervals of completely inverted position with the head and trunk dependent over the side of the bed Also in extensively paralyzed and respirator patients frequent changes in *position are required to minimize* the danger of pulmonary infection and to prevent the development of decubiti

Routinely the standard type of hospital bed is prepared by placing boards between the spring and a firm mattress A vertical

footboard blocked away from the foot of the mattress, a distance of approximately 4 in, serves the double purpose of providing a flat surface against which the feet can be maintained at a 90° angle to the long axis

greatly to comfort Small pads under the knees and the small of the back in the supine position and under the dorsum of the foot and anterior aspect of each shoulder when the patient is prone can be justifiably used early in the clinical course if these relieve discomfort Towel rolls or sandbags are used to prevent lateral rotation of the legs The upper extremities are placed at the sides or are slightly abducted with the elbow joint extended It should be remembered that variations from these standard positions are frequently necessary in individual circumstances

Green has divided the clinical course of poliomyelitis into the acute febrile stage, the sensitive period of convalescence beginning approximately 48 hours after the return of the body temperature to normal the asensitive period of convalescence which may last as long as 16 months and finally the chronic stage We are here concerned with the first two subdivisions of this classification The application of physiotherapy in the febrile stage is limited to relief of discomfort Subsequently in the sensitive period of early convalescence efforts toward the control of pain are continued but in addition particular attention is directed toward the prevention of deformities and toward the promotion of optimal conditioning of all muscles in expectation of restored innervation and the disappearance of tightness

In accomplishing the first of these ends namely, the relief of pain heat is still the most effective form of therapy Green has shown that moist heat applied to the skin is capable of increasing the temperature of underlying musculature as much as 6 to 10° F In addition to relieving the subjective discomfort, there is a marked increase in the volume of circulation to the part Equally interesting is the further observation that this elevation of muscle temperature continues for 2 to 3 hours after the pack is removed, provided the extremity is covered by the bedclothes Moist heat can be provided by the Kenny type of wrap-around pack which is cut to fit the skeletal part to be treated or by so called lay-on packs, and also by hot baths The choice of the particular form of heat to be used can then depend on individual treatment situations Wrap around packs have the disadvantage of being costly and difficult to apply properly Lay-on or prone packs need not be specifically cut to fit individual patients and are easily applied by a single person The patient is placed in a face down position in preparation for the procedure One large pack, carefully tucked around the sides of the body, is used for the neck, trunk and buttocks, while similar rectangular packs are applied to the entire extent of each lower extremity The same materials are used in each type of pack Two layers of woolen blanketing are taken from boiling water and carefully wrung out These are applied to the part as hot as the patient will tolerate, care being taken to avoid wrinkles and are covered with a waterproof material such as koroseal An outer layer of insulation usually dry flannel is finally applied There is now general agreement that packs three or four times daily for 30 minute periods are the maximum necessary (Green and Gucker), and that a sleeping patient

applying moist heat, but are not generally practical until convalescence has been well established Further, personnel and equipment for transporting the patient must be available A Hubbard tank is ideal for this form of hydrotherapy, but a large bath tub also will serve the purpose Luminous heat is recommended by some (Hayne), but is not as effective as moist heat and is not widely used

Other physiotherapeutic procedures, notably passive exercises, are not undertaken until after the temperature has returned to

daily Active exercises and muscle stretching are delayed until the asensitive phase of *convalescence has been reached*

Medication The advisability of routinely

to mind If penicillin is chosen it is logical to choose a long acting preparation in order to reduce to a minimum the number of necessary injections The possibility of orally administered aureomycin ultimately becom *ing the drug of choice seems likely*

The question of sedation is among the most pressing and difficult problems in caring for seriously ill patients Extreme caution should be the keynote of our thinking in this connection There is now abundant evi dence of widespread damage to the central nervous system in poliomyelitis Damage to medullary centers has been demonstrated at necropsy in patients who had shown no clini cal signs of such localization The imposition of further depression on already damaged centers may be crucial Restlessness and ir rationality can be erroneously interpreted as indications for sedation In the presence of these findings almost universally the need is for oxygen not sedatives Certainly every attempt at improving aeration and oxygena tion of the blood should be made before sedatives are given This will be discussed further in connection with hypoxia Occa sionally severe headache or pain in tight muscles incompletely relieved by heat inter feres sufficiently with rest as to demand attention Not infrequently 10 to 15 grains (0 6 to 1 0 gm) of acetylsalicylic acid will *control symptoms to the point where rest is* possible Barbiturates such as phenobarbital and seconal in doses of ½ to 1½ grains (32 to 100 mg) may be necessary and can be given with relative safety in most instances Rarely small doses of demerol may be justi fiable as suggested by Horstmann Morphine and codeine should not be used

Attempts at the control of spasm by the use of drugs has not been particularly suc cessful Derivatives of curare have been strongly advocated by some (Ransohoff) but must be given with extreme care since the margin between the dosage producing ade quate *relaxation and that causing paralysis* is narrow If excessive doses are given arti

ficial respiration is frequently requirec Because of the associated dangers plus th *fact that considerable doubt as to the useful* ness of the drug is reported (Richards et al) it is not recommended for general use I 1943 Kabat and Knapp introduced the us

subcutaneously is recommended Althoug reported results vary considerably there i general agreement that moist heat is mor efficacious and to be preferred At least i can be said that further studies of prostig mine are necessary before its general accept ance can be advised A final approach to th problem of directly and quickly relievin spasm has been through the production o a paravertebral sympathetic block (Collin et al) Here too only further experience can disclose the efficacy of this procedure in the treatment of poliomyelitis

The use of one additional type of medica tion should be mentioned before concluding this portion of the discussion The reduction of excessive secretions would seem to be de sirable in patients having difficulty in swal lowing as a result of lesions in the cranial nerve nuclei Atropine or ephedrine has been used occasionally for this purpose in the past The practice is mentioned only to condemn it In actuality the net result of atropine administration in this circumstance is the increased viscosity of previously more fluid secretions without important reduction in their quantity As a consequence the pa tient who is already having trouble clearing his airway of secretions *experiences greatly increased difficulty*

Respiratory Obstruction and Failure Mortality rates in poliomyelitis as reported from various epidemics range from 5 to 25 per cent *Almost without exception in fatal* cases cervical spinal cord lesions resulting in paralysis of the principal muscles of respira tion and/or lesions in the cranial nerve nuclei and respiratory center of the medulla giving *rise to airway obstruction or respiratory fail* ure are present In order to discuss therapy in this group properly let us first consider briefly the causes of their common difficulty namely inadequate oxygenation of the blood or hypoxia Elam has suggested that the respiratory difficulties in poliomyelitis can be

divided into two general categories Ventilatory deficiency is the first of these and refers to faulty transport of gases between the lungs and surrounding atmosphere It is found when there is paralysis of the intercostal muscles or diaphragm when the respiratory center is depressed, and when obstruction of the upper airway is present The second category is alveolar deficiency or insufficient transfer of oxygen from the alveoli into the blood Pulmonary edema atelectasis and pneumonia all produce this effect Not infrequently components of both ventilatory and alveolar deficiency are present concurrently in the same patient

Four general means of clinical management are available in combating improper oxygenation from these causes They can be listed as follows

(1) Artificial respiration
(2) Suction of secretions from the airway
(3) Tracheotomy
(4) Oxygen administration

It is quite apparent that an individual exhibiting paralysis of the muscles of respiration needs only the mechanical support to respiration supplied by a respirator If however, respiratory failure is the result of central depression it has been stated that the respirator is of little value Our own experience, supported by spirometric studies (Grulee et al) however does not lead to the same conclusion The usual objection

the contrary, in the presence of central respiratory failure, mechanically induced respiration should be employed if the minute respiratory volume is inadequate and if oxygen alone does not correct clinical evidences of hypoxia If the patient in question also gives evidence of innervational defects of the hypopharynx the need for artificial respiration remains unchanged but before it can be instituted tracheotomy is usually mandatory The indications for this procedure will be discussed later

Too little definitive information is available concerning respirator management Although the suggested ranges for pressure and rates of cycling the mechanism are given at 0 to 20 cm of water negative pressure, and 18 to 24 respirations per minute (Wilson), adjustments for individual patients within these limits have been reached empirically Drinker, who perfected the first

equally true at the present time, as Elam has pointed out The axiom of adjusting the respirator to the comfort of the patient must be supplanted by more exact standards since settings which result in hyperventilation are usually chosen by the patient If continued,

interpreted incorrectly as evidence of insufficient ventilation Further after the body has adjusted to a lowered carbon dioxide tension any decrease in ventilation gives rise to subjective symptoms These in turn may be attributed to inadequate ventilation and lead to a completely erroneous adjustment of the respirator The periodic determination of the carbon dioxide combining power, pH, serum protein and chloride content of the

method of following respirator patients is the determination of minute volumes of respiration by using a standard B M R machine (Grulee et al) The mouthpiece is replaced by an oronasal mask and the reservoir filled with oxygen or air (usually the former) The inspiratory tidal volume is determined by measuring the upward deflection of the writing point with each respiration These are totaled for a one minute period to obtain the minute volume of respiration The technic can be repeated as often as desired whether the respirator is operating or not, and in most situations gives an objective criterion for judging pulmonary ventilation If however, alveolar deficiency is present the minute volume of respiration will not reflect the faulty transport of oxygen from the alveoli to the blood stream Determinations of arterial

in the near future to supplant more time-

consuming and troublesome chemical analysis

Obstruction of the upper airway can be produced in one of three ways The most common is the pooling of secretions in the *hypopharynx as a result of the inability of* the patient to swallow or cough The second mechanism is closely related to the first since the presence of pooled secretions may lead to reflex closure of the glottis Finally, upper airway obstruction infrequently is produced by the apposition of the vocal cords in the midline as a result of partial though not complete paralysis, of spasm of their associated musculature

The mechanical removal of secretions requires continual alertness by a trained observer, and is greatly aided by proper postural drainage A constant source of mechanical suction such as is offered by any one of several commercially available units is satisfactory The negative pressure should be set at 5 to 7 lbs per square inch and a *catheter used as a suction tip The latter* should be provided with several openings in the distal ¼ in of its extent, and the end should be carefully inspected for sharp edges Mechanical abrasion of mucous membranes by the tip of the catheter as well as by ap-

every effort is made to avoid its prolonged use at any one time This is of especial importance when aspiration is being accomplished through a tracheotomy cannula, in which case a maximum of 2 minutes should not be exceeded In convalescent bulbar patients it is often expedient and probably desirable for the patient to carry on necessary aspiration himself In this circumstance, a curved metal tip, as is used in anesthesia, may be preferred

Not infrequently suction of the oropharynx, however conscientiously applied, is incapable *of preventing aspiration of secretions* by the

. . .

realized, however, close teamwork with an experienced laryngologist minimizes this hazard The decision as to when aspiration of secretions through the natural airway should be abandoned in favor of the more radical procedure of effecting tracheotomy or introducing an endotracheal tube cannot be arbitrarily reached on the basis of one or two clear cut signs Rather, all aspects of the immediate clinical picture and reasonable predictions for the immediate future are carefully considered Certainly tracheotomy should be performed as early as possible if its need can be anticipated By the same token, the mere presence of clinically demonstrable lesions of the glossopharyngeal and vagus nerves is not an indication since *a majority of these will recover without* surgery (Grulee and Panos) If however, an individual is experiencing a fulminant illness of short duration with steadily increasing evidences of bulbar damage, tracheotomy should be performed in anticipation of imminent central respiratory failure * and the consequent need for artificial respiration. Similarly, if definite pooling of secretions *and loss of the ability to cough are complicated* by the appearance of paralysis of the muscles of respiration of such severity that the support of a respirator is, or soon will be required, the operation must be performed If it is not, the action of the machine will necessarily lead to massive aspiration Finally, patients in whom moderately severe obstruction to the airway exists will show retraction of the intercostal spaces In the presence of this sign, even though an apparent cause of obstruction is not found tracheotomy should be seriously considered

In the preceding paragraph some of the *indications for tracheotomy based on the* presenting neurologic manifestations and objective mechanical phenomena are described Since the effect of these lesions is the production of hypoxia, it is pertinent that we direct our attention to the clinical signs of this condition One of the earliest and most helpful is an increase in the pulse rate Sometime later a moderate increase in arterial blood pressure can also be expected Irrationality and extreme restlessness are evidence that hypoxia of moderate degree is present, probably combined with some carbon dioxide accumulation Next in the sequence of increas

* The respiratory center is anatomically adjacent to the nuclei of the 9th and 10th cranial nerves

ing severity is the appearance of drowsiness Finally cyanosis and coma supervene The continued presence or progression of signs and symptoms of hypoxia not responding to oxygen therapy artificial respiration, or attempted removal of obstructions to the airway suggests the need of tracheotomy

Endotracheal intubation is infrequently employed as an alternative to tracheotomy However, the danger of damage to the vocal cords is great the tube is disturbing and uncomfortable to the patient it cannot be allowed to remain in place for more than a few hours, and, finally, it accomplishes no more than a tracheotomy does For entirely similar reasons, the insertion of 'lifesaver tubes through the larynx has been abandoned

The final tool with which we can combat respiratory failure and the effects of airway obstruction is oxygen therapy True contraindications to its use are from a practical standpoint, nonexistent The possibility of oxygen toxicity is real only if 100 per cent oxygen is breathed over long periods of time and concentrations of this magnitude are most difficult, if not impossible, to attain under the usual conditions of administration

special conditions of high grade obstruction to the airway it is desirable to employ helium with oxygen since the great diffusability of the former aids in the delivery of oxygen beyond points of obstruction

If oxygen fails to produce desired results when the indications for its use seem clearly established, technical factors are almost invariably responsible The importance of checking cylinder pressures, regulator performance, flow rate meters, humidification bottles, and oxygen lines to tent, mask or

other technics These tests should sample gas from the immediate vicinity of the patients face, since the oxygen being introduced may be displaced upward by heavier carbon dioxide which, in turn, is actually smothering the patient With some types of equipment then, flow rates must be adequate to flush out accumulated carbon dioxide or oxygen therapy is not beneficial This case is cited as an example only, and does not constitute a basic criticism of the use of tents in therapy

The administration of oxygen by nasal catheter has many advantages a minimum of elaborate equipment is necessary, the patient is more easily cared for as regards feeding aspiration of secretions, etc., and, most important, the oxygen concentration obtainable through a properly placed nasal catheter is adequate in a majority of therapeutic situations The technical details of the procedure are simple but important. In the first place, a soft 12F to 14F catheter is selected and several small apertures are made near its tip Before insertion the distance from the tip of the nose to the tragus *of the ear is measured on the catheter The* tube is then introduced to this depth or until gagging or gulping occurs It is then withdrawn approximately 1 cm and fastened securely in place Flow rates of 4 to 6 liters per minute using this method can be expected to yield up to 60 per cent available oxygen concentrations If the patient in question has been subjected to tracheotomy, the catheter may be introduced into the inner cannula In the presence of pulmonary edema the intermittent introduction of oxygen under 2 to 4 cm of water pressure is highly desirable (Grulee and Elam) Although this is usually accomplished through the tracheotomy cannula, oxygen must also be given by an oronasal mask to prevent dissipation of the positive pressure upward through the oropharynx The reader is referred to source material for the technical details of the procedure

Oxygen by mask is of limited usefulness, in large part because of poor acceptance by the patient In the absence of palsies of the ninth and tenth cranial nerves, however, an oronasal mask is entirely acceptable for oxygen therapy The interesting possibility of

too remote and could furnish an efficient alternative to the conventional respirator

In conclusion, it can be said that oxygen

liberally, since, to be of greatest value it should anticipate, not follow, the appearance of severe hypoxia

CLIFFORD G GRULEE, JR

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DENGUE FEVER

The treatment of dengue is entirely symptomatic Bed rest and sponging are required during the febrile periods Aspirin 0 6 gm should be given freely to help relieve the severe headaches and bone pains Codeine in small doses, 30 mg, is useful, especiall at night When prolonged vomiting occurs morphine sulfate, 15 mg by hypodermic injection should be given Convalescence i marked by prolonged muscular and nervou asthenia A change from the hot humic tropics to a more temperate climate is helpful during this period Extended rest anc ... un prepara ... nd freedom

Prevention requires control of the mosquito vector (Zeligs et al) Because the common vector is *Aedes aegypti*, a "domesticated mosquito, the strictest attention must be given to breeding places in and around houses Eradication of the species should be the goal Personal protection by the use of nets and repellants is effective in the individual case, but these measures cannot be relied on to protect a population

Immunity following an attack is of brief duration hence epidemic dengue may recur in an area at intervals of a few years Dependable vaccines have not been developed

HENRY R JACOBS

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YELLOW FEVER

This illness has two phases an early invasive period lasting from 2 to 5 days during which the virus multiplies enormously, and a later period of intoxication due to release of products from damaged and dead cells of the liver and other organs There is perhaps no disease that deals with parenchymatous

cells so savagely and treatment can only preserve what is left

There is no specific treatment of yellow fever Immune serum although quite effective in experimental animals when given with the virus has little use in a clinically recognizable case immune serum has therefore not been made available No chemotherapeutic agent has a demonstrable effect nor is penicillin of value Streptomycin has not been reported on nor has aureomycin or chloromycetin (Perhaps newer antibiotics may appear which will be virucidal or perhaps it will be possible to alter the intracellular medium in such a way that multiplication of virus is hampered)

Supportive treatment is all that can be given to the patient *If he is seen early in the disease he may be moved a short distance to a place where he will have absolute bed rest* and better care but if he has been ill for 2 *days or more he must not be disturbed* On the first day of illness a saline purge may be risked thereafter only enemas should be employed as the need arises The severe epigastric pain and the excruciating headaches may be treated with codeine 30 mg or morphine 15 mg by mouth if vomiting has not begun by hypodermic if it has Incessant vomiting is hard to relieve cracked ice and cocaine hydrochloride ¼ grain (15 mg) by mouth and ice caps to the head and to the epigastrium may be tried The loss of blood through vomiting and by diarrhea is usually not significant but careful attention should be given to dehydration Parenteral liquids *only* should supply the need *large volumes* rapidly administered must be avoided

Some thought has been given to measures which might help to preserve the cells of the liver Sellards and McCann believed that choline hydrochloride exerted a beneficial effect on the liver in experimental yellow fever in monkeys Possibly methionine will be found to behave similarly although it is hard to believe that measures of this sort will prove significant The use of amino acid solutions intravenously is not advisable

Conservative treatment throughout is imperative Men with a large experience (Soper) dwell on this note and until some valuable *and specific measure is found the* patient will fare better if he is not subjected to random overtreatment Antipyretics and other drugs should be used sparingly Conservatism must extend well through convalescence even though recovery in nonfatal cases is amazingly rapid the patient must follow a mild regimen for several weeks after the fever has subsided

Prophylactic treatment consists in immunization Vaccination with yellow fever vaccine confers solid immunity on a high percentage of persons The administration of the vaccine is better left to organizations skilled in the practice Persons to be immunized should be sent to the medical departments of the Army or Navy to the National Institute of Health, or to the Rockefeller Institute The use of the vaccine is described in a "Form Letter" by the Surgeon General

HENRY R JACOBS

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PHLEBOTOMUS FEVER

(Sandfly Fever Pappataci Fever Three Day Fever)

Treatment of phlebotomus fever is entirely *symptomatic* The disease has *no mortality* and complications are rare Relief of the severe pains and aches is afforded by *generous* use of aspirin (0 6 gm) or of the aspirin phenacetin-caffeine compounds with an evening dose of 30 mg of codeine In rare instances the agonizing headache may be helped by lumbar puncture although this measure must be reserved for the exceptional case

Prophylaxis depends entirely on avoiding the vector of the disease the sandfly *Phlebotomus papatasii* which bites at night Fine meshed bed nets and the use of dimethyl phthalate as a skin repellent are *useful measures Attempts to create a vaccine* serum to have led only to indefinite results thus far A first attack *confers immunity for* approximately a year but subsequent attacks are milder

HENRY R. JACOBS

FOOT AND MOUTH DISEASE
(Aphthous Fever)

Foot and mouth disease in man appears only during prevalence of the disease in cattle or other domestic animals The disease is rarely fatal, and then usually only because of special circumstances The vesicular eruption on the mucous membranes of the mouth causes pain and salivation, alkaline and antiseptic mouthwashes may be employed freely to relieve the patient Cauterization of the aphthae with solid silver nitrate is helpful The symptoms of burning, paresthesia, and pain in affected areas may be alleviated by 10 grains (0 6 gm) of aspirin or 30 mg of codeine and by the application of anesthetic ointments Because the disease is highly contagious, the proper precautions must be observed

HENRY R JACOBS

LYMPHOGRANULOMA VENEREUM

The patient should be put at rest and sulfathiazole given in 1 gm doses every 4 hours Careful attention should be paid to blood levels and the blood count and urinary findings An optimal blood level of 6 to 10 mg per cent is desirable

The Frei antigen is used in treatment Gradually increasing doses are given beginning with 0 2 cc every other day for eight doses Roentgen therapy has been used in markedly chronic infections Late chronic lesions, such as elephantiasis due to lymph edema caused by lymph blockade, may require surgical treatment Not infrequently anal stricture may develop and require rectal surgery, together with medical treatment Penicillin is of no avail in treatment, nor has any success been reported with streptomycin

Recently aureomycin has been reported to be beneficial in this disease, in a dose of 10 to 40 mg per day, administered intramuscularly Treatment is usually continued for one week The effect of aureomycin is most marked in the acute case, and it is possible that larger doses may be indicated to pre

dosage

In the chronic cases, 500 mg of aureom cin every 6 hours is a valuable adjunct surgical drainage of the lesions

JAMES I FARRELL

ACUTE GASTRO ENTERITIS

Acute gastro enteritis is a symptom com plex which may be due to a variety of e ologic factors Bacterial or virus infection bacterial toxins or putrefaction products food and food idiosyncracies are thought account for the majority of cases Only sym tomatic measures can be employed in trea ment since the exact cause cannot, as a rul be determined Although it is usually n necessary to make an exact etiologic dia nosis, in certain instances, such as acu amebiasis and acute arsenic or mercu poisoning it is essential for proper treatmen In all persistent cases or where there is failure of response to treatment a caref search for the causative factor must be i stituted

Nausea and vomiting and diarrhea wi intestinal cramps are the primary symptom and may each be present in various degree In mild cases the nausea, vomiting an cramps may be controlled with 10 minim of tr of belladonna given four times daily with 0 4 mg of atropine sulfate subcutan ously Paregoric, 4 cc three or four tim daily, is also effective For the diarrhea, bi muth subcarbonate, kaolin, or kaolin pect mixtures are satisfactory Fluids and foo should be strictly limited for 6 to 12 hour A light diet may then be allowed for th next day or two Treatment with castor o or other laxatives is mentioned only to b condemned

In severer cases it is necessary to emplo more strenuous measures Water and sa loss should be controlled as promptly as po sible since in our experience this is the mo effective means of shortening the duration o disability as well as providing symptomati relief Deodorized tincture of opium, 1 minims as an initial dose and 5 minims ever 3 hours as necessary, is most satisfactory fo this purpose Occasionally hypodermic medi cation is necessary In this case 15 mg o morphine and 0 4 mg of atropine can b used When vomiting or diarrhea has been excessive or is persistent 1000 cc of 5 pe

cent glucose in normal saline should be administered by vein

The patient should be kept in bed for 24 hours As soon as the nausea has subsided small amounts of fluid and soft light foods may be offered Sufficient medication should be given for several days to prevent a recurrence of symptoms During convalescence diarrhea may be controlled as in the milder cases

RICHARD B CAPPS

ACUTE INFECTIOUS HEPATITIS AND HOMOLOGOUS SERUM HEPATITIS

Prophylaxis Acute infectious hepatitis is contagious through the fecal oral route and consequently appropriate isolation measures are indicated Only scant data are available regarding the persistence of the virus in the feces but in most cases 4 weeks of isolation are probably adequate In homologous serum hepatitis the virus is not found in the stool so that isolation is unnecessary However there is no reliable method of distinguishing between the two types unless the incubation period is definitely known

Both strains of the virus can be transmitted by parenteral inoculation of as little as 0 01 cc of infected blood plasma or serum This danger is greatly enhanced by the presence in the population of a significant number of individuals (possibly 5 per cent) who carry the virus in their blood In addition unrecognized mild acute cases may serve as donors Nevertheless most cases due to parenteral transmission are preventable

At present no satisfactory method is available for sterilizing whole blood for transfusions although the use of nitrogen mustard is promising A calculated risk must be taken and adequate indications must be present to justify the risk of hepatitis Careful donor selection is helpful but does not eliminate the risk Donors with a history of previous jaundice or of a recent acute illness should be rejected A thymol turbidity and an icterus index can easily be performed with the routine Kahn test

Pooled plasma and convalescent serum are

needles and syringes is readily prevented by autoclaving or adequate boiling This includes equipment used to draw blood as well as that used to give injections Special attention must be directed to the technic of capillary puncture for ordinary blood counts The use of individual autoclaved or boiled knife blades is recommended Ordinary alcohol sterilization is grossly inadequate

Finally the multiple dose per syringe method of administering such medications as *penicillin or vaccines is dangerous* Infected serum may be drawn up when the plunger is pulled back to ascertain that the needle is not in a vein and thus contaminate the remaining doses

Prevention of infectious hepatitis may also be accomplished by the administration of 10 cc of gamma globulin within 10 days after exposure It is of no value after the appearance of symptoms Such passive immunity is effective for about 6 weeks

Active Treatment The active treatment of acute infectious hepatitis and acute serum hepatitis is identical since they are caused by closely related strains of a filtrable virus and present essentially similar clinical pictures Since at present there is no antibiotic or other specific substance available which is known to be effective against the virus therapy is limited to supportive and symptomatic measures designed particularly to protect the liver cells and to aid in regeneration However it must be made clear as we have shown that proper treatment will sharply reduce the severity and duration of illness as well as the incidence of residuals and in some cases is lifesaving

The principal pathologic lesion occurs in the liver and consists of injury to the parenchymal liver cells with a variable degree of necrosis and with associated inflammatory changes Although this process is well established when symptoms first appear it con

tion explains why early treatment is so important Acutely injured liver cells are peculiarly susceptible to additional noxious agents or procedures But more important it indicates why the maximal severity of the disease cannot be predicted until the crisis

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Recently aureomycin has been reported to be beneficial in this disease, in a dose of 10 to 40 mg per day, administered intramuscularly Treatment is usually continued for one week The effect of aureomycin is most marked in the acute case, and it is possible that larger doses may be indicated to prevent relapses It would seem advisable to use 500 to 750 mg of this drug every 6 hours by mouth, to supplement the intramuscular dosage

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The principal pathologic lesion occurs in the liver and consists of injury to the par enchymal liver cells with a variable degree of necrosis and with associated inflammatory changes Although this process is well estab lished when symptoms first appear it con tinues to progress during the preicteric stage and probably does not become maximal until some time between the appearance of jaun dice and the onset of recovery This situa tion explains why early treatment is so important Acutely injured liver cells are peculiarly susceptible to additional noxious agents or procedures But more important it indicates why the maximal severity of the disease cannot be predicted until the crisis

is past Thus all cases must be treated as potentially severe until recovery has set in

Our specific treatment in the different stages of the disease is as follows

Preicteric and Acute Icteric Stages Probably the most important single therapeutic measure in viral hepatitis as seen in civilian practice is bed rest It should be instituted as early as possible preferably at the time of onset of symptoms when the diagnosis is first suspected and not yet established Bed rest should be continued for a minimum of 3 weeks or until convalescence is well advanced as indicated in a subsequent paragraph If feasible lavatory privileges should be denied particularly during the initial and acute stages

The importance of the diet in civilian practice *is difficult to evaluate On theoretical* grounds we believe that it is desirable to employ a moderately high protein (100 to 125 gm) high carbohydrate (250 to 300 gm) *and a moderately low fat (60 to 80 gm) diet* If this diet can be taken there is no evidence that the addition of lipotrophic factors such as methionine or choline is of any additional value In our diet the protein is largely beef and casein the latter in the form of milk with a casein concentrate added and cottage cheese Although the role of fat is not clear from a practical point of view meat fat is poorly tolerated and a diet too low in fat is unappetizing Thus we allow enough fat mostly in the form of butter or butter fat to make the diet appetizing

In cases with nausea or vomiting persisting for more than a few days it is desirable to provide protein and sugar by vein This can be accomplished with amino acids plasma or serum albumin and daily intravenous injections of 1000 cc of 10 per cent dextrose in water

The addition of vitamins is necessary only when nausea and vomiting are persistent Excessive doses are undesirable

In the early stages of the disease fluids are of the greatest importance From a symptomatic point of view fluids should be forced either by mouth or by vein 3000 to 4000 cc daily This will usually result in a sharp abatement of symptoms especially a decrease in or disappearance of nausea Salt must not be given by vein unless vomiting is severe since it leads to fluid retention As little as 3 liters of normal salt solution intravenously has been observed to produce ascites and large pleural effusions It is desirable to restrict salt in the diet but any tendency toward fluid retention should be treated by a low salt diet

Additional liver trauma is to be avoided All drugs which are potentially hepatotoxic are contraindicated Alcohol in any form must be strictly prohibited Opiates and the short acting barbiturates since they are normally excreted or detoxified by the liver have a more prolonged action and more pronounced effect than in normal individuals and should *therefore be used with caution* if at all Atropine sulfate (0 4 mg) can be employed for abdominal cramps Salicylates increase the prothrombin time and should be *avoided in cases of severe liver injury*

During the initial and acute stages of viral hepatitis even minor surgical procedures may be fatal If surgery cannot be avoided *local anesthesia should be used since* most inhalation anesthetics are toxic to the liver

Intercurrent infections are to be avoided and promptly treated When specific measures for such complications are necessary penicillin is definitely preferable to the sulfonamides Finally intercurrent diarrhea must be promptly controlled if necessary by the use of 10 minims of deodorized tincture of opium three times daily If constipation is present and requires medication laxatives especially saline cathartics should not be used some form of enema is preferable

Acute Liver Failure When the severity of the disease is such that acute liver failure develops certain additional therapeutic measures are indicated This situation is best recognized by a drop in the prothrombin level to less than 50 per cent of normal in the presence of an adequate amount of vitamin K or by a drop in the urea nitrogen Small daily doses (5 to 10 mg) of parenteral vitamin K should be given Continuous oxygen is advisable The possibility of hypoglycemia must be considered and if found to be present treatment with continuous intravenous glucose should be instituted Hemorrhage due to decreased prothrombin in spite of adequate vitamin K can be controlled only by repeated small transfusions of whole blood

CONVALESCENT STAGE The primary problem during the stage of convalescence is the question as to when the patient should be allowed out of bed. In our opinion this should not be done until the following criteria have been met

(1) Icterus index normal for at least 10 days or, better, a normal prompt direct van den Bergh reading for 10 days,
(2) An absence of subjective symptoms, especially anorexia, increased flatus lassitude, and right upper quadrant and right lumbar ache,
(3) Absence of liver tenderness on fist percussion and of tenderness in the right costovertebral angle, liver size approaching normal
(4) Bromsulfalein dye retention (5 mg per kilogram dose) less than 5 per cent in one hour or 7 per cent in 45 minutes other liver function tests approaching normal

If only one of these criteria cannot be met, the patient can be allowed up after one extra week of bed rest Caution must be employed in dealing with individuals over 40 years of age, cases with history of previous liver disease, or individuals who have had a particularly severe or prolonged illness After being allowed up, patients should be observed for a period of at least 4 weeks If during this time liver tenderness reappears, or if the laboratory findings become significantly increased, the patient should be returned to bed for a period of at least 3 weeks

SUBSEQUENT TREATMENT Patients should not be allowed to return to strenuous work for a period of at least 2 weeks after getting out of bed, and preferably for a period of one month Regular work can then be resumed, providing findings continue to be normal Alcohol should be prohibited for a period of at least 3 months It is probably best to maintain a reasonably high protein diet for this period

RICHARD B CAPPS

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DISEASES DUE TO BACTERIA

THE PNEUMONIAS

Since 1935 type specific antipneumococcus serum, sulfonamides of many types, penicillin, streptomycin aureomycin and other less widely known agents have been added to the physician's therapeutic attack on pneumonia Also a distinct shift in the incidence of the various types of pneumonia has occurred It is now of much more than academic interest to diagnose accurately each patient with pneumonic consolidation as to etiology and extent of invasion and associated pathologic changes

While many cases of pneumonia (or pneumonitis) are *primary* in the sense of being initial infections due to invasion of highly virulent micro-organisms, especially pneumococci and viruses, there are a great many others in which a particular set of circumstances makes it possible for micro-organisms leading a more or less saprophytic existence in the respiratory tract to invade the lung parenchyma Unless these predisposing conditions are recognized and combated along with active antibacterial therapy some failures will result

In every case of pneumonia, whether hospitalized or cared for in the home, in addition to a painstaking history and physical examination, a careful bacteriologic examination of the sputum and blood *prior* to instituting

sable in estimating the extent of parenchymal involvement, especially in the early stages of all pneumonias Often it too may be done in the home A sudden onset with pleural pain blood tinged sputum, and a chill, particularly if accompanied by leukocytosis and the presence of pneumococci in smears of the sputum is sufficient for the establishment of a working diagnosis of pneumococcus pneumonia and institution of therapy for that disease pending the results of sputum

and blood culture On the other hand an insidious onset with scanty physical findings at the start scattered areas of increased density throughout the lungs as shown roentgenographically and a normal or decreased leukocyte count are strongly suggestive of one of the virus pneumonias for which antibacterial therapy can be expected to do no more than prevent secondary bacterial invasions

Prophylaxis NONSPECIFIC MEASURES Awareness of the common predisposing conditions to the development of pulmonary infection is the first step in prevention These conditions include among others (1) *all* infections of the upper respiratory tract particularly those due to the pneumococcus (2) *those conditions which promote pulmonary* congestion and underventilation such as cardiac decompensation heavy sedation particularly following operation nephritis with edema peritonitis shock from any cause poliomyelitis involving the respiratory muscles (3) pulmonary embolism (4) obstructive lesions in the bronchial tree (5) trauma to the thoracic cage (6) allergic pulmonary edema The implications of the above considerations are obvious

Value of Cultures of Nose Throat and Sputum Smears and cultures of the nose throat and sputum and a leukocyte count are prerequisite to proper management of all respiratory infections whether pneumonia has developed or not If these reveal large numbers of pneumococci hemolytic streptococci if *Streptococcus viridans* is found in *the nose or if there is a high leukocytosis* the indication for sulfonamide or penicillin in full doses is clear *Hemophilus influenzae* and *Klebsiella pneumoniae* infections of the respiratory tract may respond better to streptomycin

Prevention of Pulmonary Congestion The necessity for prompt digitalization and oxygen therapy for patients with cardiac decompensation and for penicillin therapy if such patients have even mild colds is being better appreciated In the same way senile and postoperative patients should not be allowed to lie passively *in one position which* combined with shallow breathing soon results in passive hyperemia of the lungs then bronchopneumonia In addition to being forced to get out of bed at the earliest possible moment that their general condition permits such patients frequently benefit from 5 to 10 minutes of carbon dioxide administration every hour to promote hyperventilation

Present interest in phlebothrombosis has made physicians aware of the need for prompt anticoagulant therapy when that condition is present or imminent and for the ligation of veins which have been the site of thrombosis as well as sulfonamide or penicillin therapy when pulmonary embolism occurs

Removal of Bronchial Obstructions The improvement following prompt removal of bronchial obstruction is so spectacular that it

dren the exudate in bronchi and bronchioles is so abundant and extensive that asphyxiation results from this mechanical interference with oxygen reaching the alveoli rather than from filling of the alveoli with fibrin plugs In postoperative or postpartum aspiration of stomach contents or inhalation of foreign bodies severe pneumonitis is almost certain to follow if relief of the obstruction is delayed Prompt bronchoscopic aspiration followed by antibacterial therapy is urgently indicated

Prevention of Posttraumatic Pneumonia Phillips has recently called attention to the high incidence of pneumonia following nonpenetrating chest injuries According to his figures 2 per cent of all primary pneumonia cases at the Permanente Hospital Foundation are posttraumatic In the majority the consolidation developed at the site of trauma while in about 30 per cent it was at the site of the "contrecoup" pulmonary injury When there is severe trauma to the chest Phillips recommends papaverine hydrochloride 30 mg and atropine sulfate 0 4 mg intravenously every 4 hours for 2 days following injury to prevent reflex pulmonary atelectasis Relief of pain should be by procaine infiltration rather than by the use of sedatives and measures should be taken to in

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prophylactically are also important All suggestions are timely and might well be

extended to all patients with severe injuries, particularly if they are elderly and have lain on the ground long enough to reduce body temperature In such persons, it is always wise to delay any operative procedure that can be delayed until the potential post traumatic pneumonia has been aborted.

Combating of Allergic Pulmonary Reactions In the management of highly allergic individuals known to be sensitive to feathers, dust, and other allergens, it is well to remember that such persons are often equally sensitive to bacteria Therefore, if a bacterial infection initiates or accompanies severe allergic rhinitis or bronchial asthma iodides in full doses to keep bronchial secretions thin enough not to occlude bronchioles, aminophylline to dilate the bronchioles, and antibiotics or sulfonamides to combat the infection are usually in order

SPECIFIC PROPHYLAXIS While it is obviously impossible to produce specific active immunity against all of the micro organisms that may cause pneumonia, certain measures are distinctly helpful

MacLeod and his associates and Walter Schenkein, and Sutliff have shown that a single subcutaneous injection of small amounts of the various specific polysaccharides of pneumococci produces a good immunity against these types of pneumococci but not others

On the basis of reports of its efficacy in Army personnel, widespread immunization with vaccine prepared from influenza virus A and B has been accomplished in the United States Among the few reports from responsible investigators have come indications that the incidence of influenza A and B and pneumonia accompanying these infections has been greatly reduced among the immunized persons It is well to remind pa

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termine The author's own impression is that they are of distinct value in persons who possess bacterial allergy In such persons who have repeated respiratory infection, an autogenous vaccine, made from streptococci pneumococci or *Hemophilus influenzae* cultures from the nose, throat, or sputum, administered in small desensitizing doses over a period of several months, has, at times, given welcome relief

Active Treatment of Pneumonia At the present time, few patients who are even suspected of having pneumonia escape penicillin, aureomycin, or one of the sulfonamides This procedure is defensible because practically all bacterial pneumonias are benefited by these measures, and in the virus infections probably some secondary bacterial invasion is prevented However, since the kidney complications of sulfonamide therapy are common and other complications by no means rare, these drugs should not be continued for long periods unless the need for their use is clear Complications of penicillin therapy are less serious, but allergic reactions to it are becoming more frequent The difficulty of administration and the cost of the antibiotics also are considerations which cause one to weigh the need carefully before ordering them

ANTIBIOTIC THERAPY *Penicillin* Penicillin is useful against all of the pneumonias caused by gram positive cocci, particularly pneumococcal pneumonia, and psittacosis It may have some specific effect in the other ornithosis pneumonias, but actual proof is lacking Also when one is in doubt as to the etiology, and bacterial pneumonia seems a strong probability, penicillin is the agent of choice In older persons with hypertension or arteriosclerosis and in any individual with known renal impairment it should, if pos

responses from its use

At present there is widespread interest in developing the most convenient and economical dosage compatible with clinical effectiveness In the near future some revision of present concepts may have crystallized enough to merit general acceptance However, from present evidence the safest way to be sure of controlling bacterial growth in pneumonia is to administer the penicillin in *aqueous solution*, using a physiologic solution of sodium chloride as the diluent, in

fewest reactions, sulfadiazine is the sulfonamide chosen by most physicians Sulfamerazine, its isomer, appears to be equally efficacious The blood level of sulfadiazine can usually be maintained in adults at 5 to 10 mg per cent or above by 1 gm every 4 hours by mouth after an initial dose of 2 to 4 gm, but in occasional patients with excellent renal function, the dose must be higher Of course, in others, too high a blood level is reached on this schedule and the dose must be decreased In most cases requiring intravenous injection of the sodium salt, 2 gm every 6 hours or 3 gm every 8 hours are about right Sulfamerazine is excreted more slowly After an initial dose of 2 gm in the adult an effective blood level may usually be maintained by 1 gm every 6 hours by mouth though this dose at 4 hour intervals is usually well tolerated When intravenous administration of the salt is required, 2 gm every 8 hours is usually adequate These doses may be given directly into the vein in 5 per cent solution or added to a venoclysis of 5 per cent glucose in water or of physiologic solution of sodium chloride When sodium salts of sulfonamides are added to alkaline solutions, the drug will be precipitated

If sulfathiazole is the sulfonamide chosen, the dose must be larger After an initial dose of 3 or 4 gm, the maintenance dose, early in the course of bacterial pneumonia, usually should be 1 5 to 2 0 gm every 4 hours if renal function is unimpaired Even with this dose, it is sometimes impossible to maintain a blood level as high as 10 mg per cent, but a lower blood level is often effective There [illegible]

peatedly emphasized, but it is sufficiently important to bear repetition It still seems not to be well understood that *large* doses of sodium bicarbonate are required to keep the urine at a pH of 7 5 which is a fairly safe level In our experience, 16 to 24 gm by mouth, per 24 hours is required, making an oral dose of about 3 0 gm every 4 hours If the patient cannot take the alkali by mouth, he should receive 1 liter of ⅛ molar sodium lactate solution every 24 hours by vein

Recently a new sulfonamide, 3, 4 dimethyl 5 sulfanilamide isoxazole, which has been given the trade name of *gantrisan*, has been released for clinical use (Rhoads et al) It has practically the same range of clinical usefulness as sulfadiazine and is given in the same dosage, but is many times more soluble in the urine Unless the patient's fluid intake is inadequate, an alkaline adjuvant need not be given with it It also has the advantage that its salt as the diethonalamine *is not irritating and may be given intramuscularly* in concentrations as high as 40 per cent solution The writer's experience with this drug in bacterial pneumonia is limited. But if it proves as efficacious in large series of cases as the early work indicates, in time it probably will replace sulfadiazine and sulfamerazine because of its greater safety

Biologic Therapy Since the advent of sulfonamides and penicillin, specific antipneumococcic rabbit serum is seldom used. However, at the height of the interest in its use many dramatic cures were effected without any other antibacterial therapy In desperate cases, if the pneumococcus can be typed and type specific serum obtained it may be the factor which tips the balance in favor of recovery In one case of hemolytic streptococcus pneumonia, scarlet fever convalescent serum in a dose of 200 cc intravenously appeared to be the factor which, in addition to sulfadiazine, produced a favorable outcome In one of the writer's most severe cases of atypical primary bronchopneumonia, in which the issue was uncertain for several days, a blood transfusion from a patient recently recovered from this disease appeared to be a lifesaving measure We have not used Alexander's *Hemophilus influenzae* serum in the pneumonias associated with this organism, but from experience with this serum in *Hemophilus influenzae* meningitis, one would be tempted to use it in a critical case if streptomycin were not controlling the infection The writer has used staphylococcal antitoxin in only one case of staphylococcal pneumonia, without a favorable result However, this agent is of some value and should be considered in patients failing to respond to penicillin and sulfonamides

General Measures Of the general measures to be used in pneumonia, complete rest

in bed is probably the most important Observations have shown that pneumococcal pneumonia patients properly treated are incapacitated for about one half the period as patients with viral pneumonia The prolonged prostration which follows the latter type is probably its most serious feature The exact time at which pneumonia patients may safely leave their beds and later resume their normal activities depends on the judgment of the physician in each case It should never be before 3 full days without fever have elapsed Many patients with primary atypical bronchopneumonia have been incapacitated for as long as 6 weeks Those with bacterial pneumonia properly treated may at times be back at work 2 weeks after the onset

Pulmonary Edema One serious condition frequently appearing in respiratory infections and particularly pneumonia is the intense pulmonary edema which occurs suddenly in patients in whom previously the manifestations have been relatively mild When this edema occurs because of a failing myocardium the situation is serious Probably the somewhat outdated practice of phlebotomy should be used more often in these cases to reduce the load on the right heart Even if it is not used more care should be taken than is usually done to avoid increasing this load by giving large amounts of fluids intravenously and by guarding ag

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of decompensation The digitalizing dose of

0 2 mg daily is usually sufficient It is now well established that simple tachycardia of the type accompanying any severe infection is not in itself a reliable indication for digitalis

When the pulmonary edema is due to an intense allergic reaction it is usually more easily controlled than when the cause is decompensation Aminophylline 0 25 gm for adults administered slowly by the intravenous route usually gives the most prompt relief This should be followed by potassium iodide in doses of 8 to 12 drops of the saturated solution three or four times daily and aminophylline by mouth If the patient is unable to take it by mouth 1 0 gm of sodium iodide in 10 per cent solution may be given intravenously Adrenalin 3 to 5 minims of a 1 1 000 solution subcutaneously of course gives prompt relief in bronchial asthma but there are more dangers of serious reactions in hypertensive and other cardiovascular patients than when intravenous aminophylline is used

Oxygen Administration Oxygen in dosage to the point where cyanosis is fully relieved

capillaries is greatest in "wet pneumonias with large amounts of secretion in the bronchioles particularly if circulation through the lungs is impaired by a failing heart Also if consolidation is quite extensive cyanosis usually is present The method of oxygen administration is a matter of individual preference Introduction by nasal catheter is probably the most efficient and economical Usually the catheter is put into one nostril far enough so that its tip appears just beyond the free edge of the soft palate It is changed from one nostril to the other every 12 hours The writer uses a modification of this technic suggested by Krasno The catheter tip is inserted into a hole cut in the center of a small piece of sponge rubber which has been trimmed to fill one nostril snugly The catheter is pushed only far enough so that the tip clears this rubber collar Thus irritation from the catheter lying in the floor of the nostril is avoided When

about 8 liters

For patients who do not tolerate the nasal catheter well the oxygen tent should be used Unless a rubber sheet completely covers that portion of the mattress which forms the floor of the tent and the skirts of the tent are tucked under the mattress and bedcovers snugly much oxygen will be lost Usually a flow of about 12 liters per minute is required to maintain an oxygen concentration of 50 per cent which is considered desirable The oxygen concentration should be checked every 8 to 12 hours so that the proper flow can be gauged if possible

Meteorism Meteorism often proves to be a serious problem in patients who are extremely toxic Prompt and abundant oxygen administration is the most efficacious way of combating it In addition, hot stupes to the abdomen enemas to empty the colon of feces high rectal tubes through which gas may be expelled or siphoned off and injection of prostigmine 1 cc of the 1 2,000 dilution all are measures which may help

Control of Cough The cough of pneumonia may be a troublesome feature It is part of the mechanism of ridding the bronchioles of exudate and should not be entirely suppressed If the sputum is extremely thick and tenacious potassium or sodium iodide in doses of 8 to 15 drops of the saturated solution in ½ glass of water will reduce the viscosity appreciably For a painful hacking cough codeine sulfate or phosphate in doses of 30 mg every 4 to 6 hours is the best remedy It may be given in conjunction with elixir of terpin hydrate A favorite prescription of the writer s is

Syr ipecac } Syr squill }	—aa	drams i
Morphine sulfate		grains ii
Elixir terpin hydrate		ounces vi

Sig 1 Teaspoonful every 3 hours for cough

Codeine may be given separately in addition to this It must be remembered that if more than two doses of codeine per 24 hours are required constipation may become a problem

Pleural Pain Pleural pain should if possible, be relieved by aspirin or phenacetin compounds in the usual doses with the occasional addition of codeine Heat to the affected area usually helps If these measures fail, strapping the chest with adhesive may be required This should be avoided if possible because it obscures the physical signs

Dehydration Dehydration may become a problem in pneumonia because the patient may be too sick to call for water himself Water or fruit juices or weak tea up to a minimum of 2500 cc every 24 hours for adults during the febrile period should be insisted on If the patient cannot take them by mouth, intravenous fluids may be required When sweating has been quite profuse 1 liter of physiologic solution of sodium chloride or Ringer s solution may usually be given safely The remainder of the day's requirements should be 5 per cent glucose in water or amino acids in glucose solution *Fluids must be given slowly* because of the danger of increasing the load on an already overburdened heart

COMPLICATIONS Of these empyema is probably the most common When this condition is strongly suspected thoracentesis should be done promptly As much of the purulent fluid as possible should be aspirated and 50,000 to 100,000 units of penicillin introduced into the cavity before withdrawing the needle If frank pus is present, surgical drainage after rib resection usually should be done Occasionally, when treatment has been prompt, repeated evacuations through the needle along with penicillin in full doses will effect a cure

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often serve as the foci for metastatic lesions in the brain and meninges

Bacterial endocarditis, usually pneumococcal when a sequel of pneumonia, is an extremely serious complication When the diagnosis is established doses of penicillin not less than 1,000 000 units per day given in equal doses every 2 hours day and night, should be used if the offending organism is penicillin sensitive

For the rare endocarditis case due to gram negative bacilli, a correspondingly high dose of streptomycin is in order

Pneumococcal or streptococcal meningitis as a sequel of pneumonia has a bad prognosis Treatment is discussed in the following sections

PAUL S RHOADS

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MENINGOCOCCAL MENINGITIS *

which the meningococci find their way into the blood stream to attack the meninges

General Treatment Because this is the only form of meningitis designated as communicable the patient should be isolated and the case reported to the local health officer Confinement in a darkened room is not necessary Good ventilation is important, and the principles of medical asepsis are particularly essential during the first few days of illness It is a good practice to have restraints on every meningitis patient Sedatives are not always required but if they are morphine should never be used Sodium phenobarbital or sodium amytal in doses appropriate to the age and condition of the patient is usually satisfactory An ice bag to the head is sometimes helpful

DRUGS The sulfonamides are now universally used for therapy Antisera are not likely to be available even if desired as adjuvants Penicillin is not an important accessory for treatment of the ordinary form of meningococcal meningitis Nevertheless with massive doses (1 000 000 units daily) recovery with penicillin alone is possible It is useful for some of the complications Penicillin should never be given intrathecally Its introduction in this manner may result in disastrous consequences (Hoyne and Schultze) some of which recall earlier days when intraspinal serum was a routine procedure Sulfadiazine is undoubtedly the drug most commonly selected while sulfanilamide rarely receives any consideration Sulfapyridine has declined markedly in popularity, but sulfamerazine has some advantages not possessed by the other sulfa drugs Warnings have been issued persistently by manufacturers of sulfathiazole (Hoyne and Grossman) and by others not to use this drug for the treatment of meningitis The chief objection set forth is that sulfathiazole does not readily enter the cerebrospinal fluid Nevertheless our experience has been that even though blood levels and consequently spinal fluid levels for sulfathiazole are lower than with any of the other sulfonamides the results of treatment are equally as good if not better Combinations of the sulfonamides are also obtainable in tablets consisting of

sulfadiazine 37 per cent Favorable and unfavorable opinions have been expressed in respect to their superiority over a single sulfonamide Their purpose is to lessen the likelihood of damage to the kidneys

* At the time of this writing fe v reports indicat ng the value of aureomyc n and chloromycetin in the treatment of bacter al meningitis ha e appeared Evidence indicates that both of these antibiot cs traverse the blood bra n barrier and diffuse readily into the cerebrospinal fluid For this reason it v ould seem likely that both of these agents may in the near future assume an important place in treating infections of the central nervous system — *Ed tor*

The dose is usually determined on the basis of body weight, administering from 1 to 2 grains per pound, according to the severity of the infection The estimated amount constitutes the total dose for the first 24 hours of treatment The initial dose would then be one half the total, and the remainder divided into five equal parts, given at 4 hour intervals, until the drug is discontinued This method of figuring dosage may be suitable for a child However, it is apparent that in the case of adults it would often result in excessive estimates Therefore it has been [illegible]

weight of the patient Even for an infant, our initial dose of a sulfonamide is seldom less than 2 gm followed by 1 gm at 4 hour intervals for 3 to 4 days and then reducing [illegible] factor [illegible]

those over 10 years the initial dose is generally 5 gm, irrespective of the sulfonamide selected In extremely severe infections the initial dose is sometimes repeated after a lapse of 2 to 4 hours and rarely 2 gm are administered at 4 hour intervals for 2 or 3 days and then reduced to 1 gm until discontinued when the temperature has remained normal for about 48 hours The average number of days for sulfonamide therapy is usually 5 to 8

FLUIDS AND ALKALIES Before beginning sulfonamide treatment, it is well to administer fluids and to see that the patient receives from 500 cc to 3000 cc daily, depending on age and whether a state of dehydration is present During the first few days much of [illegible] parenterally For the [illegible] dis- [illegible] is is [illegible] often placed on the necessity of an alkali when prescribing a sulfonamide Sodium bi- [illegible] al to each dose of [illegible]

of the latter is sometimes estimated on the basis of 1 cc per kilogram of body weight However, it has seemed to the writer that the volume of fluid intake is of more importanc than the alkali in preventing unfavorabl reactions from the sulfonamides

ROUTE FOR ADMINISTRATION OF SULFONA MIDES If the patient is an adult and rationa the drug may be given orally For infant and young children, oral administration i often unsatisfactory The drug may not b swallowed or emesis may occur without th knowledge of the physician As a conse quence, the patient with no benefit from th drug fails to improve or rapidly loses ground To avoid such possibilities, some physician resort to gavage or adopt the stomach tube to which there are numerous objections Sul fonamides have also been given by rectum an unsatisfactory procedure Two thoroughl reliable routes for giving sulfonamides whe oral administration is not feasible are th intravenous and the subcutaneous In eithe instance one can be assured that the drug will be retained

At the Municipal Contagious Disease Hos pital, Chicago, and for patients on my service at Cook County Hospital, the routine plar is to inject the initial dose of the sulfonamide intravenously The sodium salt of the drug in 5 per cent solution is given in norma saline by the drip method Almost any promi nent vein is suitable for insertion of the needle, but a vein near the bend of the elbow, at the ankle, or the dorsum of the foot is usually selected For the administra tion of an initial 5 gm dose of sodium sulfa diazine, the 5 gm will be in a flask containing 100 cc of normal saline, to make the 5 per cent solution of the drug It will require about one hour for the patient to receive this treatment, the time depending on the rate of flow Generally, allowance is made for 20 to 40 drops a minute The arm or leg in which the needle is inserted should be firmly immobilized on a splint and the latter se curely attached to the bed, in order that the needle does not become displaced or blocked by blood The latter may happen if the flow is too slow Frequent attention should be given to this matter If the patient is in a comatose condition and continues so for sev eral days, it may be necessary to repeat in travenous medication a number of times [illegible] of cases oral [illegible] 24 hours [illegible] itial dose

ometimes it is difficult to pierce an infant's ein without a "cut down," a procedure often ollowed in our contagious disease hospitals To circumvent this requirement, the sulfonamide can be injected subcutaneously with atisfactory results, even when given at 6 to 3 hour intervals The sodium salt is used for ubcutaneous injection as well as for intravenous and can be given in either a 5 per ent or sometimes only a 2 5 per cent so ution

A blood level should be obtained within 24 hours of beginning treatment If more onvenient a sample of blood may be sent o the laboratory much earlier The first blood level following the initial treatment is ikely to be higher than those that follow, but not always so A reading of 20 mg per 100 cc of blood is often expected, and it is hoped that when sulfadiazine is the drug concerned that a level of from approximately 10 to 12 will be maintained It is advisable to obtain two or three readings a week When sulfathiazole is used it will be found that blood levels are generally consistently low Sometimes levels for this drug do not exceed 4 and rarely rise above 8 but the patient progresses favorably, nevertheless In many hospitals daily or frequent spinal taps are made in order to determine sulfa levels in the cerebrospinal fluid However, it has been shown that spinal fluid levels range ordinarily from 50 to 70 per cent at most of the blood levels Therefore, from a practical standpoint, lumbar punctures are not a necessity for such a purpose Some clinicians also wish a daily determination of the sugar in the spinal fluid, because its rise or fall is valuable as a prognostic sign With such a routine, variations in the spinal fluid cell counts may also be noted and the presence or absence of organisms determined From a scientific standpoint it is interesting to

physician should be able to assure himself from clinical signs, without contributory evidence from the spinal fluid, whether or not the patient is responding to treatment A complete blood count should be made before beginning treatment and a white blood count obtained at least once a week There should be also a daily urinalysis, including a microscopic examination for blood and also sulfa crystals

Meningococcemia Patients with a bacteremia are treated as described for the ordinary form of meningitis All procedures are

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blood culture has been secured or if meningococci have been obtained on smear from petechiae in the skin, a lumbar puncture is not essential

Chronic meningococcemia without meningitis is a rare condition If inadequately treated it may continue for several months with periodic showers of petechiae The treatment is the same as for acute meningococcemia, although large doses of penicillin may be added

Nasopharyngitis If a known contact develops a 'sore throat" it should be assumed, until proved otherwise that a meningococcal infection is responsible Prompt institution of treatment may abort a serious illness before the organisms gain entry to the blood stream One gram of sulfathiazole or sulfadiazine orally three times daily for 3 days may be sufficient

Fulminating Form Many such cases are patients with the so called *Waterhouse Friderichsen syndrome*, with massive hemorrhages into the adrenals There may also be minute hemorrhages throughout the tissues

regarded as inevitably fatal, a number of recoveries have been reported in recent years One of the primary purposes of therapy for such infections is to combat shock The patient should be wrapped in warm blankets and the foot of the bed elevated An aqueous solution of adrenal cortical extract, 5 cc given intravenously for the first dose, is thought to be helpful Doses of the same drug in amounts of 2 cc are then given intramuscularly from two to four times daily Sodium sulfadiazine, 5 gm, or sodium sulfa-

and plans made for a blood transfusion of 50 to 150 cc If whole blood cannot be secured readily, plasma is a good substitute If possible an oxygen tent should be used

CARRIERS Known carriers seldom develop the disease because they are usually immune Nevertheless they may transmit the infection to others Therefore anyone proved to be a carrier should be isolated and treated with a sulfonamide until negative cultures have been obtained from the nasopharynx Two gm of a sulfonamide twice a day for three days should be sufficient When a meningococcal meningitis patient is found in a household it is likely that some or even all contacts may be infected even though none develops meningitis But whether infection has actually occurred or not prophylactic measures should be adopted Generally 5 gm of sulfathiazole or sulfadiazine orally twice a day for 3 days is satisfactory for protection

COMPLICATIONS Since intrathecal therapy for meningococcal meningitis has been largely abandoned though involuntarily because of the sulfonamides complications have declined precipitously Deafness and loss of vision which formerly were fairly common are now seldom observed when there is prompt diagnosis and early treatment When deafness does occur it is generally bilateral and if complete there is small chance that hearing will ever be regained There is no satisfactory treatment However if some hearing remains marked improvement may eventually take place Among 233 patients treated with antiserum intrathecally some years ago in one of our contagious disease hospitals there were 20 with complete loss of hearing What is sometimes re

doses of penicillin sometimes 500 000 to 600 000 units daily It should be injected intravenously as well as subcutaneously Krause has given penicillin for endophthalmitis by means of iontophoresis with good results An effort should be made to keep the pupil dilated with atropine 0 25 per cent and 1 or 2 drops of 15 per cent argyrol in the eye daily may be of value Panophthalmitis with destruction of one or both eyeballs is extremely rare

Arthritis is the commonest complication and suppurates only occasionally when the knee joint is involved It can be treated by means of immobilization and salicylates

Hydrocephalus formerly common in infant is extremely infrequent if there has been n intrathecal therapy Frequent lumbar pun tures for drainage will not improve th condition Endocarditis and pericarditis wi effusion are both rare and likely to be fata although we have had 2 recoveries from th latter

Aside from bronchopneumonia and occ sionally lobar pneumonia most of the othe complications including brain abscess su purative otitis media various forms of par sis mental retardation and changes i personality are rare With modern metho of treatment the duration of illness is s shortened that decubitus ulcers are seldo encountered

TOXICITY OF SULFONAMIDES Sulfadiazin is responsible for more hematuria than an of the other drugs considered here It is als more likely to cause blocking of the ureter with crystals and produce anuria Sulfamera zine has come next to sulfadiazine in ou experience in the frequency with which i causes hematuria Yet the total amount o sulfamerazine required to bring about re covery is less than with other sulfonamide Sulfapyridine was accompanied by less hema turia than either of the preceding two drug but gave poorer therapeutic results Sulfa thiazole caused about one third as muc hematuria as sulfadiazine and there are usu ally fewer skin rashes than from sulfadiazin or sulfamerazine Sulfanilamide is seldo used now for the treatment of meningit but it is less irritating to the kidneys tha the other drugs referred to However ther is often cyanosis and it may produce psych disturbances In our contagious disease hos pitals neither nausea nor vomiting has bee a prominent manifestation of toxicity from any of the drugs named The possibility o agranulocytosis should always be considered especially if the drug is prescribed for a unusually long period The foregoing opin ions concerning the sulfonamides are based on an experience with the treatment of ap proximately 1 500 patients

COMMENT Except for the purpose of di agnosis intrathecal punctures are not required in connection with the treatment of meningitis This is not because of the intro duction of the sulfonamides and other anti biotics As early as 1934 Hoyne at Cook

ounty Hospital, discontinued all intrathecal herapy for meningococcal meningitis and ave all antisera intravenously With that nethod the fatality rates were equally as ow as they are today with the newer drugs Therefore, it seems to be evident that an mportant contributing factor in reducing nortality by means of the sulfonamides is he absence of intrathecal therapy

In 1936, the writer reported 76 meningo-occal meningitis patients with a case fatal ty rate of 11 7 per cent, treated with ntiserum by the intravenous method ex-lusively In 1948, Hoyne and Brown re orted 727 patients with a fatality rate of 14 8 per cent, treated with sulfonamides, and only 22 of the number had any intrathecal herapy The fatality rate for the group of 22 vho received penicillin intraspinally in ad-lition to sulfonamides was 40 9 per cent

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INFLUENZAL MENINGITIS

Hemophilus influenzae (Pfeiffer's bacillus) type B must not be confused with epidemic influenza, which is caused by a virus The etiology of this infection and its route of invasion are extremely important from a therapeutic standpoint Although clinical evidence of meningitis may become evident with a violent abruptness, there are sometimes warning signs to prepare the experienced physician for what may follow At the onset of infection, difficulty in breathing caused by edema about the glottis and epiglottis may lead to a suspicion of laryngeal diphtheria or laryngotracheobronchitis Moreover, it soon becomes apparent that emergency measures must be adopted to relieve impending asphyxiation Signs of respiratory obstruction in infants and children under 5 years of age, should always lead one to think of the possibility of a type B *Hemophilus influenzae* infection, and under such circumstances a blood culture should be obtained In many instances the organisms pass from the nasopharynx into the blood stream, but with prompt diagnosis and treatment the infection may be subdued without indications of the meninges becoming involved

Under the circumstances set forth, emergency treatment may demand an immediate tracheotomy If the edema about the glottis and epiglottis is not too marked, an intubation will occasionally suffice, if performed by an experienced operator Streptomycin in doses of 100,000 micrograms should be prescribed at once and be administered intramuscularly at 3 hour intervals In addition, it is well to give from 1 to 2 gm of sodium sulfadiazine in 5 per cent solution in normal saline intravenously by the drip method

taneous, and it is often satisfactory to give the drug in this manner at 6 to 8 hour intervals instead of 4 For those who prefer, dosage of the sulfonamide may be determined according to body weight, which would call for from 1 to 2 grains per pound

for total dosage during a 24 hour period The entire estimated dosage would then be divided into an appropriate number of equal parts according to the time intervals established for this medication

Within 12 to 24 hours after having carried out the procedures described evidence of meningeal irritation may develop, and it becomes apparent at once that the patient is suffering from meningitis However, it must be remembered that meningitis may develop without any respiratory embarrassment A lumbar puncture should be performed and *the spinal fluid will probably be cloudy and* a laboratory examination should disclose gram negative, pleomorphic *Hemophilus influenzae* No additional intrathecal taps are likely to be required during the course of treatment This statement is made notwithstanding the insistent advice to the contrary which has been given and continues to be repeated by clinicians with experience As a rule, 5 days of streptomycin treatment should be adequate However, the sulfonamide *should rarely be discontinued in less than* 2 weeks and a longer period may be necessary For infants under one year of age it is also often well to administer intravenously by the drip method 50 to 100 mg of type B anti influenzal rabbit serum This serum may be given in from 50 to 100 cc of normal saline, to which are added 5 to 10 minims of adrenalin It is particularly desirable to give

are likely to be at their height When using type B anti influenzal serum it is advisable *to request the* laboratory to make quellung tests with blood serum in order to determine if response to the antiserum is satisfactory However, it is not imperative to perform quellung tests with cerebrospinal fluid Consequently, there should be no occasion for making daily lumbar punctures for such a purpose Nor are frequent spinal taps required with the *object* of determining whether there is a rise or fall in the spinal fluid sugar If the patient is not responding well to treatment, transfusion of from 50 cc to 200 cc of whole blood may be of great benefit If there is evidence of pneumonia or the patient is in a desperate condition it is advisable to inject intramuscularly approximately 30,000 units of penicillin at hour intervals and place the patient in a *oxygen tent A few clinicians (Solovey)* believe that penicillin may be of some therapeutic value in the treatment of influenza meningitis This is undoubtedly true if the patient is treated intrathecally because the penicillin may combat secondary invader if they are introduced by numerous lumba punctures

Complications In most instances whe convulsions occur it is during the first fe days of the disease but rarely they ma *come on later Chloral hydrate, 5 to 10 gram* (300 to 600 mg) by rectum, may be helpful Phenobarbital sodium, in doses of ½ to grains (30 to 120 mg), depending on th patient s age and the severity of the attack sometimes proves to be satisfactory, if repeated when indicated Other medication which may be used for the same purpose include seconal, 1½ grains (90 mg), sodium amytal, 2 grains (120 mg), or ether inhalations Magnesium sulfate in 25 per cent solution *is sometimes effective when injected* intramuscularly in 5 cc doses

Facial paralysis strabismus and paresi of one or more extremities are other complications for which there is no specific treatment Generally such conditions improve progressively as the patient approaches recovery Extreme irritability is noted more often in this kind of meningitis than in any other In infants especially, mental retardation must be considered among the possibilities, *if there are sequelae*

Toxicity of Drugs It is well recognized that streptomycin may be responsible for *certain toxic reactions* The most common is labyrinthine disturbance which usually disappears completely within a period of 3 weeks from the time that treatment was *started* Deafness, often feared is a much more serious complication because there is always uncertainty regarding the ultimate outcome in respect to regaining the hearing If there is prompt discontinuance of the drug the chance of permanent impairment is lessened Skin rashes from streptomycin are *rare* but indurated areas at the point of injection are not unusual Chills fever, nausea and vomiting have been observed Renal damage is also said to occur rarely *and has* been attributed to unduly high levels of strep-

tomycin, or in those receiving the drug intrathecally or in unusually large doses over a prolonged period Stomatitis (Beham and Perr) has also been reported as a manifestation of streptomycin toxicity The frequency of hematuria as a result of sulfadiazine therapy has been discussed under the treatment of meningococcal meningitis The importance of adequate fluids has been stressed and the use of alkalies referred to It is impossible to state too emphatically that the intrathecal administration of streptomycin is not imperative for successful treatment of influenzal meningitis, and many admit the severity of its toxic reactions when given by this route Nevertheless, the Division of Medical Sciences of the National Research Council stated in January 1948 that, Better results have been reported in patients with bacterial meningitis given streptomycin intrathecally as well as intramuscularly than in those receiving it intramuscularly only '

Those who persist in giving streptomycin intrathecally have reported fatality rates of 20 per cent and state that 'Such excellent results emphasize the necessity for injecting streptomycin intrathecally" In referring to this mortality figure (20 per cent) in their recent book, Keefer and Hewitt also say "The necessity for administration of streptomycin both intramuscularly and intrathecally for the treatment of meningitis is well known" It is unfortunate that everyone does not know that intrathecal therapy is not required for the successful treatment of meningitis The same authors recommend intrathecal therapy for at least 4 to 7 days and "advisedly 10 to 14 days are necessary to obtain the best response to treatment and to prevent recurrences of meningitis due to occasional reinoculation of the meninges from intrameningeal foci which continue to harbor viable bacteria" This sentence is descriptive of what occurred when meningococcic meningitis was treated with serum intrathecally Hoyne and Brown reported 30 consecutive cases of influenzal meningitis with a fatality rate of 6 7 per cent Only 6 patients in the entire group received streptomycin intrathecally in addition to intramuscularly, and only 2 deaths occurred among those 6 Most of the 30 patients had but a single lumbar puncture, which was performed for the purpose of establishing a laboratory diagnosis

All strains of *H influenzae* are not pos- [illegible]

sulfadiazine, or to both In 1941, Hoyne reported 16 *recoveries from influenzal meningitis* There was no streptomycin at that time, nor was there available any sulfadiazine for these patients Seven of the number were given serum Three of those who had serum received no sulfonamides Six were treated solely with sulfapyridine 5 with sulfapyridine and sulfanilamide, and one exclusively with sulfanilamide Of the entire group it [illegible]

of tuberculous meningitis Even at the beginning of the sulfonamide era, recoveries were few As late as 1940, Sirlin and London stated, "Until the present time only 5 cases [illegible]

rate of 54 per cent

At present streptomycin is granted superiority over any other single agent for the [illegible]

annual meeting of the American Academy of Pediatrics, held in November 1948, Alexander had an exhibit in which was shown a series of 30 patients treated exclusively with streptomycin Twenty two described as having mild or average attacks made good recoveries However, the 8 patients who had severe infections died Apparently, all pa [illegible]

cally twice daily for 10 days and intramuscularly every 3 to 4 hours A sulfonamide was also given orally in "high doses" There were 12 deaths, a fatality rate of 40 per cent, and the author calls attention to the "high percentage of recoveries ' given as 12, as 2 additional survivors had sequelae

Recently, Levinson reported 60 cases of influenzal meningitis treated according to different methods Depending on the drug or combination of drugs fatality rates ranged from 100 per cent for 6 patients receiving sulfonamides alone, to no deaths for a group of 17 treated with streptomycin intramuscularly and sulfadiazine, but without any intrathecal therapy He definitely decided that intrathecal streptomycin was unnecessary, thus confirming the contention of the writer

Based on our own experience, and that of others, there seems to be no doubt that the treatment of choice for influenzal meningitis consists of both streptomycin and sulfadiazine Moreover, it appears probable that each of these remedies can be administered at more extended intervals with satisfactory results If such is the case, patients would suffer less discomfort and much time would be saved by the nursing service in a hospital Even now it has been maintained that the total 24 hour dosage of intramuscular streptomycin can be given in a single daily injection without loss of the therapeutic effect gained from divided doses Moreover, there are indications that 2 or 3 days' treatment with streptomycin will prove to be adequate in the management of influenzal meningitis when sulfadiazine is prescribed at the same time and continued for approximately 2 weeks Consequently, efficient treatment may become still more simplified for those patients who do not receive intrathecal therapy Nevertheless, because some strains of *H influenzae* are resistant to streptomycin, it may become necessary to take advantage of type B anti-influenzal rabbit serum as an additional aid If laboratory facilities are available, the sensitivity of *H influenzae* to streptomycin and to the sulfonamide employed in treatment should be determined in every case

With early diagnosis and prompt institution of appropriate treatment, the recovery rate for influenzal meningitis should now approximate 90 per cent

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PNEUMOCOCCAL MENINGITIS

For many years the mortality for this form of meningitis approximated 100 per cent Hewell and Mitchell reported that for 10 years preceding 1937 there were in the Children's Hospital in Cincinnati 23 cases of pneumococcal meningitis, all of which were fatal During a period of 25 years the writer saw only 2 recoveries at the Cook County Hospital However, when type-specific antipneumococcus rabbit serum became available the prognosis brightened About 4 years later (1937) sulfanilamide was introduced, and with the broadening recognition which these two remedies received the number of deaths from pneumo

treated during 1938 and 1939 Therapy consisted of the specific type of antipneumococcus serum intravenously and either sulfanilamide or sulfapyridine This group of patients is mentioned particularly here because no intrathecal medication was given Sulfapyridine appeared on the market shortly after sulfanilamide, and enhanced still fur

ther a favorable outcome Other sulfonamides have been introduced since, including sulfadiazine, sulfathiazole, and sulfamerazine, and any one of these singly or in combination may prove suitable for attack against the pneumococcus

In 1941, Hoyne reported 14 recoveries All but 2 of the patients received a specific type of antipneumococcus serum intravenously Every patient was treated with a sulfonamide which was usually sulfapyridine No patient received intrathecal treatment Six patients each had but a single lumbar puncture, which was made for diagnosis The largest number of spinal taps for any patient was four, which were done only in one instance There were no recurrences or sequelae The youngest patient was 5 years and the oldest 76

Penicillin Since the introduction of penicillin fatality rates for pneumococcal meningitis have declined considerably, but are seldom less than 50 per cent, and may be much higher for infants Moreover, sequelae develop among some who survive Hutchins and Davies reported 14 cases ranging in age from 6 weeks to 13 months Treatment consisted of penicillin intramuscularly, 3000 to 5000 units every 3 hours, and intrathecally 10 000 units twice daily This therapy was continued on an average of about 10 days Type-specific serum was also given in 4 cases and sulfadiazine in 11 There were 5 fatalities and 4 were apparently cured The remaining 5 had varying degrees of central nervous system damage Ross and Burke had much better results with 19 patients treated with combined sulfadiazine and penicillin Sixteen recovered with penicillin administered intrathecally as well as intramuscularly The authors state that the penicillin produced no irritation Sodium sulfadiazine with a dosage based on 2 to 3 grams (60 to 90 mg) per pound of body weight for each 24 hours was given at 8 hour intervals, in ⅙ molar lactate, 5 per cent dextrose in Hartman s or in saline solution Type specific antiserum was used routinely in the first 7 patients, but no conclusion is drawn regarding its value Three of the surviving patients had residual central nervous system sequelae One patient had relapses

Intrathecal Therapy Relapses and recurrences are not unusual with intrathecal treatment and would undoubtedly occur more often with the use of penicillin alone than when combined with a sulfonamide Boines expressed himself as favorably impressed by our method of treating meningitis without intrathecal therapy He reported 3 cases of pneumococcal meningitis with recovery One of the 3 had no intrathecal treatment He states, "Because of the host of possible complications from multiple spinal taps emphasis is placed on a minimum number for diagnosis and therapeutic procedures "

Nearly all reported recoveries from pneumococcal meningitis have had intrathecal treatment This route is often adhered to even though shock, convulsions, paralysis, and secondary infections lead to a form of meningitis that the patient did not originally have and even to death Hoyne and Schultz reported a patient who had five attacks of meningitis over a period of approximately 5 years A different organism was responsible for each episode On the first four occasions the patient was successfully treated without intrathecal therapy For the fifth attack penicillin was given intrathecally and after 4 days of such treatment an extensive subarachnoid hemorrhage developed, which was directly responsible for the man's death

At the Municipal Contagious Disease Hospital (Chicago) during a 6 year period from 1942 through 1947 there were 68 admissions with pneumococcal meningitis Thirty of the patients recovered without intrathecal therapy This makes a fatality rate of 55 8 per cent which is not remarkable, but is equally as good as most similar series of patients which have been reported The ages ranged from 2 months to 74 years Eighteen of the

cocci This entire group was treated without penicillin intrathecally and there were 14 recoveries The authors make no reference to a previously reported large series of meningitis patients treated without intrathecal therapy Nevertheless it is gratifying that they seem to have become convinced that meningitis patients can make good recoveries without intrathecal therapy However, a lack

of confidence is displayed in the reliability of that plan because they believe "intrathecal penicillin should be reserved for those who do not respond to adequate systemic therapy"

Focus of Infection Before beginning treatment it is often not merely interesting but also important to determine the focus of infection In many instances there appears *to be no doubt that the ear is the port of* entry for the pneumococci In others the primary focus is a bronchopneumonia or a lobar pneumonia Just as with meningococcal meningitis, a large percentage of pneumococcal meningitis patients will have a positive blood culture We have also observed on numerous occasions that patients with pneumococcal meningitis give a history of trauma about the head Surprisingly often recovered patients have stated that they experienced a skull fracture, not recently, but one or more years in the past Patients who have a skull fracture seem to be particularly susceptible to meningitis which is not always caused by the same organism Two of our patients at the Municipal Contagious Disease Hospital who gave histories of having had fractured skulls experienced second attacks of pneumococcal meningitis, and on each occasion a different type of pneumococcus was cultured from the spinal fluid At the Cook County Hospital we treated one man successfully on four occasions and he gave what appeared to be an authentic history of three previous attacks This last named patient had his first attack of meningitis following a skull fracture which occurred in 1941 and his last hospital admission was in 1948

Routine Treatment The routine treatment for pneumococcal meningitis need be no different from that for most other forms of meningitis In every instance a blood culture should be obtained and a lumbar puncture made in order to establish a reliable [illegible]

called in consultation to determine whether or not surgical intervention is indicated There need be no delay in instituting treatment because the typing of organisms is no longer a necessity and a specific type of antipneumococcus serum is practically unobtainable Proper treatment demands adequate amounts of penicillin and one of the sulfonamides As with other forms of meningitis, it is often well to administer the initial dose of the selected sulfonamide intravenously For the average adult 5 gm of the sodium salt of sulfadiazine, sulfathiazole or sulfamerazine in 5 per cent solution in normal saline can be given by the drip *method, and the time required for this procedure* will approximate one hour The initial dose should be followed at 4 hour intervals, by from 1 to 2 gm, depending on the severity of the case Ordinarily, 1 gm every 4 hours is sufficient If the patient is rational and not vomiting the dose of sulfonamide may be given orally Otherwise it may be necessary to continue the drug by vein We believe there are objections to the use of a stomach tube for the introduction of *the sulfonamide, and that resort to this* method should as a rule, be avoided In the case of children, either a 5 per cent solution or sometimes only a 2 5 per cent solution of the sodium salt of the drug can be given subcutaneously With the subcutaneous route sufficiently high levels of the drug may be maintained when this medication is administered at intervals of 8 or 12 hours This is especially true if sulfamerazine is the drug employed Penicillin should be given in large doses, both intravenously and intramuscularly Generally at least 25 000 units and possibly four times that amount may be injected intramuscularly at 3 hour intervals In addition, from 200,000 to 500 000 units may be needed for intravenous administration every 24 hours for 2 or 3 days Within 12 to 24 hours after the beginning of treat*ment it is advisable to determine* the blood level of the sulfonamide, and this should be done two or three times a week It is well to maintain a level of from 10 to 15 mg per cent for most of the sulfonamides However, when sulfathiazole is used blood levels are likely to be much lower, and yet the patient progresses as favorably as when other sulfonamides are given and higher levels are obtained The importance of adequate fluid intake and output must have critical attention at all times An adult will usually require daily approximately *3000 cc* of fluid parenterally The question of giving an alkali should always be considered even

though the quantity of fluid intake may be more important For alkalinization purposes equal quantities of sodium bicarbonate may be given with each dose of the drug when the patient is able to take oral medication Otherwise, $^1/_6$ molar sodium lactate on the basis of approximately 20 cc per kilogram may be given intravenously daily

Sometimes nothing is more effective for the patient who is making slow progress than a blood transfusion The amount of cit rated whole blood to be given will depend on the age and sometimes the condition of the patient Generally the quantity will range from 50 cc for an infant to 500 cc for an adult Plasma may also be used for the same purpose in corresponding doses In addition glucose in either 5 or 10 per cent solution in distilled water or normal saline is likely to be a daily requirement

As in other cases where a sulfonamide is prescribed, a complete blood count and urinalysis should if possible be made prior to starting treatment Under any circum stances a white blood count should be made

sulfa crystals determined If hematuria de velops it is sometimes advisable to substitute a different sulfonamide should it be felt that

rted that
n readily
enters the cerebrospinal fluid, organisms dis appear and patients make good recoveries without intrathecal treatment It should be remembered that concentrations of sub stances in the spinal fluid are dependent on the concentration of those substances in the blood stream and the permeability of the barrier Permeability of the barrier is in creased during an attack of meningitis Al though in the past there was often much concern in regard to intracranial pressure and the demand that it be relieved by fre quent lumbar punctures and drainage much less thought is given to this matter now Frequent lumbar punctures seem to stimu late the secretion of cerebrospinal fluid and headache is complained of more often be cause the intrathecal tap affords only tem porary relief

Treatment should be continued until the patient is clinically well and the temperature has remained normal for at least 2 days Many will desire an additional lumbar punc ture for cerebrospinal fluid examination be fore the patient is discharged from the hospital

Prognosis An opinion regarding the out come of the illness can often be formed fol lowing the initial and perhaps only lumbar puncture required when an examination of the spinal fluid is made A high cell count with few organisms is favorable whereas a low cell count with numerous organisms

though some clinicians desire daily lumbar punctures for frequent examinations of the cerebrospinal fluid in order to determine the sugar content in particular such a procedure is by no means a necessity

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STREPTOCOCCAL AND STAPHYLOCOCCAL MENINGITIS

Streptococcal Meningitis Sometimes it is difficult to realize that less than 10 years ago the prognosis of nearly every form of bacterial meningitis, with the exception of the meningococcal, was almost certainly hopeless Sappington and Favorite, in a review of the literature in 1939, made the

comment "Meningitis produced by the streptococcus pneumococcus staphylococcus influenza bacillus and tubercle bacillus as well as some rare organisms is almost universally fatal regardless of the treatment" Among the various forms of pyogenic meningitis streptococcal and staphylococcal organisms may be grouped with the lesser offenders In a review of the literature to 1935 Gray found only 65 cases of reported recoveries from streptococcal meningitis and added his own case However all of the recoveries that have been reported were not due to hemolytic streptococcus but included nonhemolytic as well Presumably only a small portion of the total was due to *Streptococcus viridans* However in an investigation of this subject by Hoyne and Herzon (unpublished) it has been interesting to note that in recent years at the Cook County Hospital while hemolytic streptococcal meningitis appears to be much less frequent than formerly the percentage of streptococcal meningitis which is due to the *Streptococcus viridans* is greater

Recoveries from streptococcal meningitis have been so unusual (Felsen and Osofsky) that single instances were reported Marick reported a nonhemolytic case in 1936 with recovery His treatment consisted of spinal drainage every 8 hours for 4 days then twice daily for 5 days and then once Since the sulfonamides came into general use the mortality from streptococcal meningitis has declined somewhat Among Sappington and Favorite s 22 reported cases of meningitis which were treated with sulfanilamide 6 were due to hemolytic streptococci and 4 of these recovered There were also 2 instances of *Streptococcus viridans* meningitis with one recovery Formerly whether with or without major surgical intervention entailing drainage there were usually numerous intrathecal punctures made for the relief of intracranial pressure and examination of the cerebrospinal fluid On occasions blood transfusions and human convalescent scarlet fever serum were used in the hope of preserving life

Streptococcal meningitis seems to occur more often by direct extension from a suppurating ear or mastoid infection than by way of the blood stream from a focus in the nasopharynx The former route of invasion was on occasion noted in the past in our contagious disease hospitals Therefore when streptococci are found in the spinal fluid of a patient after a primary lumbar puncture the focus of infection should be sought in the middle ear or mastoid cells Consequently under such circumstances it is advisable to have a consultant make an

preparation should be started Sodium sulfadiazine 5 gm intravenously should serve well for the initial dose and be followed by 1 gm every 4 hours The customary attention must be given to the use of alkalies and an adequate fluid intake In addition 50 000 to 100 000 units of penicillin should be injected intramuscularly every 3 hours and perhaps intravenously as well These patients may also benefit greatly from frequent blood transfusions From 50 cc to as much as 500 cc of citrated whole blood may be given every other day if the patient s condition is extremely critical

Complications If the patient survives the first few days of illness endocarditis may develop and its occurrence is sometimes announced by a shower of minute petechiae If response to treatment with sulfadiazine is poor it may be advisable to resort to sulfanilamide which at times is particularly effective against streptococci The dosage should be the same as for sulfadiazine Rarely a brain abscess may occur or a lateral sinus thrombosis may be either an associated condition or else the primary focus from which

from which the meningitis develops Notwithstanding the present armamentarium of modern drugs fatality rates in general continue to be high for this form of meningitis often approximating 50 per cent

Staphylococcal Meningitis Staphylococcal meningitis is less frequently reported than most of the other pyogenic infections

from the laboratory that the organisms found are not a contaminant Staphylococci should always be considered as the possible cause

[illegible]

sitive blood culture is an aid in substanti
ng staphylococcal meningitis when staphy-
occi have been reported in the spinal fluid
t *suspected as a possible contaminant of*
e culture A smear from the spinal fluid
less likely to be contaminated than a cul
re

In general, treatment is the same for aphylococcal meningitis as when other or- anisms are responsible for meningeal signs owever, although favorable response may *sult from the administration of any one of* e sulfonamides, sulfathiazole in this in ance seems to be preferable Penicillin hould also be prescribed in large doses tramuscularly In this manner from 50 000 100,000 units may be required every 3 ours and, in addition from 200,000 to 00 000 units intravenously daily by the drip *method Definite improvement is likely to be* vident within 24 hours after beginning the reatment There is no necessity for intra hecal therapy or frequent lumbar punctures or drainage On two occasions I have seen ecoveries brought about almost solely by neans of numerous blood transfusions In one of these instances, a 14 year old boy eceived blood intravenously on 23 occasions Staphylococcus toxoid and staphylococcus antitoxin are of doubtful value

In 1941, Hoyne reported 4 recoveries from [illegible]

occurred in a baby 3 days old Both spinal fluid and blood provided positive cultures for hemolytic *Staphylococcus aureus* The infant was treated with sulfathiazole and penicillin and discharged from the hospital in good condition at the end of 16 days There were no complications or sequelae after a period of 3 months In so far as we could determine, this was the youngest patient ever reported with staphylococcal meningitis and the only one under 2 weeks of age who survived The amount of sulfathiazole administered to this infant was 1 9 grains every 4 hours or ap proximately 0 8 gm every 24 hours which was prescribed for 15 days In this case, the dosage of the drug was based on the weight of the patient, administering about 2 grains (60 mg) per pound Contrary to our usual custom for infants, the sulfonamide was given orally because the child had constant nursing attention and it was known that the drug was swallowed and retained There were no overt reactions Every 2 hours for a period of about 2 weeks, sodium penicillin in 5000 unit doses was injected intramuscularly For the entire period of treatment the total amount of penicillin was 1,640 000 units, and the total dose of sulfathiazole was 15 gm The highest blood level obtained for the latter drug at any time was 4 0 mg per cent, which illustrates a previous reference per taining to the low concentrations in the blood when sulfathiazole is the remedy From the foregoing discussion it should not be assumed that staphylococcal meningitis is a condition found chiefly in children of tender age As a matter of fact although reported cases are not overnumerous staphy- lococcal meningitis is likely to be observed more often in adults Our oldest patient was a man of 70 years, who recovered

COMPLICATIONS With staphylococcal men ingitis there is often a presumption that if the patient survives, osteomyelitis will make itself evident in some portion of the body In reality, such a complication does not al ways occur Among a comparatively small number of cases of staphylococcal meningitis the writer has seen only 2 who presented evidence of osteomyelitis In one instance a small bone of the foot was involved, and in another there was an abscess formation in the shoulder joint with a probable osteo myelitis of the proximal end of the humerus

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TUBERCULOUS MENINGITIS

There has been perhaps no more amazing development in medical therapeutics than the discovery of an agent which is capable of retarding the progress of pathologic conditions caused by the tubercle bacillus In the past *tuberculous meningitis* was almost certainly a fatal disease It has been estimated that at least 50 per cent of infants and children who die of tuberculosis have tuberculous meningitis As with other forms of meningitis, the condition is not primary This fact is important from a therapeutic standpoint because other lesions in the body may require treatment as well as the meningitis Infection of the meninges may take place through the blood stream or by direct extension from an osseous lesion in a locality contiguous to the circulation of the cerebrospinal fluid In some instances it is believed that caseous tubercles in the brain substance may lie dormant for years before discharging bacilli into the cerebrospinal fluid A large percentage of patients who die from tuberculous meningitis have miliary tuberculosis

Streptomycin Therapy Schatz, Bugie, and Waksman's discovery of streptomycin reported in 1944 contributed the first real hope for the tuberculous meningitis patient Standardization of streptomycin was reported by Waksman in 1945 but this antibiotic did not become generally available until 1946 Now favorable reports concerning this drug as an effective agent for the inhibition of tuberculosis are multiplying almost daily But even with streptomycin extremely few claims have been made for permanent recovery from tuberculous meningitis

Among 100 patients with tuberculosis reported by Bunn 43 had meningitis without other evidence of tuberculosis Sixteen of this number were living 4 to 7 months after starting treatment with streptomycin but only 4 had completely normal cerebrospinal fluid Ten of the 16 patients showed no clinical evidence of meningitis There were 10 patients who developed meningitis during or subsequent to treatment of miliary tuberculosis Only 3 of the 10 were living 9 to 12 months after the onset of meningitis and but one of the 3 could be classed as a recovery The daily dosage of streptomycin consisted of 0 6 to 4 0 gm intramuscularly and 0 01 to 0 2 gm intrathecally Most of the patients were treated for 120 to 180 days The author believes that 1 8 gm daily is advisable for not less than 90 days and that after 120 days the majority (two thirds) of the patients becomes streptomycin resistant He states that a study of intramuscular versus intraspinal therapy for tuberculous meningitis has not appeared justifiable The patients who responded poorly were those with a disseminated tuberculosis

Alperin and Toomey reported 9 cases of tuberculous meningitis with improvement in 2 Two patients received streptomycin intrathecally and in one of these, three doses had little effect on the cerebrospinal fluid All of the other patients were given streptomycin exclusively by the intramuscular route There were 6 deaths One of the survivors was blind In another, the outcome was doubtful while in but a single instance the condition of the patient seemed to be good *Promin* was also prescribed for all patients in this group

Levinson treated 19 tuberculous meningitis patients with streptomycin intramuscularly There was only one instance where the patient also received intrathecal treatment, which was continued for 9 days Eleven of the 19 died at the time of the report 8 were still living and improved One patient was living 14 months after hospital admission Levinson states "We have learned cerebrospinal fluid takes up streptomycin when given intramuscularly" The dosage consisted of 200 000 micrograms every 3 hours for 90 days Deafness occurred in 2 patients Although there was often quick response to streptomycin therapy, as a rule there was little change in the spinal fluid which required from 3 to 4 months to become normal However, the spinal fluid glucose was sometimes normal within a few days The Levinson test remained positive for 2 to 3 months For those who progressed favorably the test became negative, but in those who did not improve the test was positive *Chlorides* were not considered a reliable guide to recovery Pulmonary tuberculosis which was present in 17 patients subsided in most cases Streptomycin levels in the cerebrospinal fluid ranged from 40 to 160 micrograms

notwithstanding that intrathecal therapy was not resorted to

Bertoye and Lantermier observed 11 cases in 3 of which there were encouraging re sults In none of these patients was there an associated miliary tuberculosis Nine of the patients were treated exclusively by intra muscular injections at first the dosage being from 1 5 to 1 gm daily later the dose was 0 5 to 0 25 gm according to weight There was no improvement in one girl and one nursling who had received intraspinal injec tions of from 15 to 25 mg of streptomycin

Since January 10 1948 12 tuberculous meningitis patients have been treated with streptomycin at the Municipal Contagious Disease Hospital (Chicago) The ages ranged from 5 months to 39 years Nine of the 12 were less than 6 years of age One was 13 and one 29 On December 15 2 pa tients were still alive One is a 2 year old Negro child who continues to be well nour ished but is apparently blind and mentally deteriorated The other is a 4 year old Negro girl whose condition seems to be good Neither patient appears to have a dissemi nated tuberculous infection but there are pulmonary findings in the younger child Tubercle bacilli were found in the spinal fluid of each patient Both of these children received streptomycin intrathecally as well as intramuscularly The younger child has been under treatment for 8 months and the older one for 2 months The immediate future looks favorable for the latter whereas for the former the ultimate prognosis is un doubtedly bad Our plan of treatment has been to administer approximately 1 gm of streptomycin daily in divided doses at 6 hour intervals intramuscularly for some patients and for others to give in addition 25 000 to 50 000 —

given streptomycin by the intramuscular route exclusively all died Nevertheless these figures are not a true indication of what may occur One patient 39 years of age who re ceived no intrathecal treatment died within 10 days another without intrathecal treat ment failed to survive throughout the day on

ment was started and the other within 6 days On the other hand a 9 month old in fant who was treated exclusively by the in tramuscular route survived for 7 months Another patient 3 years of age who had no intraspinal therapy also survived for 7 months At the Cook County Contagious Hospital the writer had a 14 year old Negro girl as a patient who had in addition ex tensive involvement of both lungs She has been treated with streptomycin exclusively by the intramuscular route intermittently over a period of 14 months Her present condition appears to be excellent Roentgeno graphic examination has shown a striking recession of the tuberculous process in the pulmonary areas her mental condition is

had relapses on two occasions During most of the time that streptomycin has been ad ministered this patient has had approximately 1 5 gm daily in divided doses at 12 hour intervals

Blood and Spinal Fluid Levels for Streptomycin Ordinarily spinal fluid levels may be expected to range from 50 to 70 per cent of the blood level when there is no intrathecal therapy For some of our patients who had exclusive intramuscular treatment with streptomycin spinal fluid levels were 25 micrograms when the blood level was 50 This ratio however was not true in all cases Nevertheless in some instances spinal fluid levels were nearly double the blood level when the levels were obtained at the same time Levinson reported spinal fluid levels ranging from 40 to 160 micrograms for pa tients who received no intrathecal therapy A number of levels obtained from our pa tients who were treated intrathecally were far lower in comparison with the blood level than for certain other patients who had no intraspinal therapy

Bunn who believes that treatment of tu berculous meningitis without intrathecal streptomycin is not justifiable, states that streptomycin is a local irritant and that intrathecal injection produces pain and on occasion paraplegia He believes these phe nomena are lessened by using slow well diluted injections of 50 mg on alternate days and that such treatment maintains

adequate concentration which should exceed 5 micrograms per cubic centimeter in the cerebrospinal fluid Other reactions from streptomycin have been reported including *fever and skin eruption when the latter* occurs eosinophilia may be present Among the more common toxic effects however are tinnitus vertigo and deafness Xanthochromic cerebrospinal fluid and agranulocytosis have also been reported

Duration of Treatment Although Bunn believes as previously mentioned that the majority of patients become streptomycin resistant after 120 days I have seen one patient treated for 5 *months continuously* who relapsed after streptomycin was stopped but responded well when the drug was resumed Just how long a patient should be *treated with streptomycin* is difficult to determine because relapses are so frequent However if the patient appears to be clinically *well and the spinal fluid has returned* to normal it seems reasonable to stop medication but to keep the patient under observation

Management of Patient The following procedures should be adopted thorough physical examination complete blood count sputum examination urinalysis and roentgenogram of chest It is also well to have a laboratory examination of stomach washings and to do a tuberculin test A lumbar puncture should then be made and an examination conducted in the laboratory for detection of tubercle bacilli If the organisms are found a guinea pig inoculation should be performed It would seem that although a sufficient number of patients has not been *treated to provide* adequate proof there is no necessity for giving streptomycin intrathecally The intramuscular dose for patients under our supervision has varied from 1 to 2 gm daily In some cases the total daily dosage has been divided into equal parts in order to give the streptomycin at 6 hour intervals *Nevertheless a satisfactory* response has been obtained when the daily quantity of streptomycin was administered intramuscularly in two equal parts at 12 hour intervals Some clinicians believe that the entire daily dose may be given in one injection Para aminosalicylic acid has been recommended as a *substitute for* streptomycin if the latter drug failed to produce a favorable response Sometimes para aminosalicylic acid is given in addition to streptomycin Pamisyl, which is manufactured in 0 3 gm tablets is a trade name for para aminosalicylic acid The daily dosage of pamisyl is 12 to 15 gm orally for an adult or 1 gm per 10 lbs of body weight for children Dihydrostreptomycin hydrochloride which is derived from streptomycin by reduction is claimed to be a potent antibiotic It is said to be as effective as streptomycin but much less toxic, and therefore can be prescribed in larger doses for longer periods It is stated further that patients allergic to streptomycin have *been able to continue with dihydrostreptomycin* This drug is stable at room temperature for one month and in powder form for 18 months In solution it can be administered in doses of 250 to 500 micrograms per cubic centimeter The minimum interval for intramuscular injections is 6 hours but 12 hour intervals are regarded as *preferable Not* more than 2 cc should be injected at any one time and two injections in succession in the same general area should be avoided The dose for children is 20 micrograms per pound of body weight Dihydrostreptomycin is said to be less neurotoxic and responsible for less vestibular and auditory dysfunction than streptomycin Moreover this drug rarely causes renal irritation and gastric disturbances

[illegible] method [illegible] peutic agents He states "By incorporating the known tuberculostatic agent on one end of a surface active molecule an increased in vitro effect on the tubercle bacillus has been obtained" He says further "It is anticipated that the more potent tuberculostatic drugs such as streptomycin could be made more effective by incorporating the *molecules into* a surface active compound"

In the brief period during which streptomycin has been employed for the treatment of tuberculosis the drug's accomplishments have been remarkable However in respect to the therapy of tuberculous meningitis far more progress must be made *before* we can assume that patients with this disease will have even a fair chance for permanent recovery

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SCARLET FEVER

Aim of Treatment The work of Lancefield and his co workers, by their exact grouping and typing of hemolytic streptococci has thrown light on the epidemiology of scarlet fever The causes of the complications relapses, and reinfections are now clearly understood

Gradually it has been realized that a hemolytic streptococcal invasion of the nasopharynx without a scarlet rash differs in no essential respect from a similar hemolytic streptococcal invasion with a rash The hemolytic streptococci which elaborate an erythrogenic toxin are necessarily not more virulent than the same type of organism which does not produce a rash

It has become apparent that poststreptococcal nonsuppurative syndromes such as rheumatic fever, glomerulonephritis and rheumatoid arthritis, follow the hemolytic streptococcal invasion of the nasopharynx in approximately 5 per cent of such infections The known antigenic properties of the type specific substance derived from group A hemolytic streptococci and the production of enzymes such as hyaluronic acid and hyaluronidase by these same organisms have brought about a realization that early and effective treatment is necessary

Treatment must, therefore, be directed toward ridding the throat of the invading organism before quantities of the antigen are absorbed, and before complications, reinfections, and relapses can occur Complications such as otitis media, may result from the primary organism Relapses and reinfections are known to follow a change in the type of the pathogenic organism

Treatment must also be aimed at blocking the antigen before the hyaluronidase (spreading factor) can carry the antigen into the mesenchymal cells If the invading organisms can be destroyed before large quantities of the antigen or enzyme and co enzymes are produced, and before a change in type takes place, the patient will be spared the suppurative complications, such as otitis media and mastoiditis as well as the nonsuppurative complications such as rheumatic fever and acute glomerulonephritis

Isolation Every case of hemolytic streptococcal invasion of the nasopharynx should be isolated The cases of sore throat which, either before or during an epidemic, show

isolated until the throat culture can be reported upon Those patients with positive throat cultures should be isolated Treatment in a common ward is undesirable, irrespective of the type of organism, stage of the disease, and possible complications Isolation is carried out in separate rooms in the hospital or private rooms at home The hemolytic streptococci are air borne, and attendants and nurses must wear nasal and mouth masks Bedclothing is oiled and all surfaces kept clean with oiled dust cloths Individual thermometers and dishes are used, and sterilized after use

Bed Rest All cases of scarlet fever are

rest is 3 weeks Severely ill patients may require much more time in bed, determined by the degree of fever, heart rate, leukocyte count, sedimentation rate, and, if nonsuppurative complications are suspected, the electrocardiogram and the antistreptolysin O titer

Fluids are forced by mouth up to 3000 cc daily If necessary to maintain this amount parenteral routes may be chosen

The diet is liberal high in calories proteins and vitamin content The form depends upon the patient s degree of toxicity

Specific Therapy *Penicillin* is the drug of choice

Penicillin given in 150 000 to 300 000 units twice daily as advocated by Jersild or *300 000 units twice daily as suggested by Massell will free the patient s throat of* streptococci in 24 to 48 hours This dosage is continued for at least 6 and preferably 10 days The patients treated for too short a time may have a recurrence of the infection since only small amounts of antibody are formed owing to the early eradication of the organisms With penicillin therapy the average febrile period is 4 to 5 days instead of the 7 to 8 days in sulfonamide treated patients The rash of scarlet fever is uninfluenced by

seen with

spond qu

per cent coming to surgery In the sulfonamide group 21 per cent of the complications come to surgery

Penicillin therapy permits home treatment of scarlet fever patients since oral penicillin 600 000 to 1 000 000 units per day is as effective in most cases as the intramuscular injection Carriers of streptococci in the home should be subjected to the same type of therapy

Sulfonamides in the form of sulfadiazine may be given to prevent the complications of scarlet fever They are best used in conjunction with scarlet fever convalescent serum Oral dosage of 1 gm per day to infants 2 gm for older children and to young adults 0 5 gm every 3 hours with equal amounts of sodium bicarbonate and large amounts of fluid are adequate doses

Scarlet fever antitoxin is of no real value 0 2 cc injected intradermally will cause the rash to blanch (Schultz Charlton reaction)

Pooled convalescent serum may be used in the highly toxic cases The serum may be obtained *from* state boards of health in emergencies The dosage varies from 10 cc intravenously in children to 80 cc intravenously in adults taking precautions against reactions

Complications The treatment of the suppurative complications is unnecessary because *most of the complications are avoided* by penicillin therapy In 2 per cent of cases surgery may be necessary

DESQUAMATION No treatment is necessary *except to give comfort If pruritus occurs* use petrolatum to the skin or a mixture of 4 parts olive oil to 1 part glycerin in dilute alcohol

SORE THROAT The sore throat requires no treatment if penicillin is used In severe cases that are seen late a warm saline gargle and saline swab applied to the nose are all that is required

OTITIS MEDIA Otitis media sinusitis and

should be performed

NEPHRITIS Nephritis usually occurs in the second to fourth week If the case is seen late and penicillin has not been used examine the urine daily for albumin and red blood cells When nephritis is discovered prolonged bed rest a low protein salt free diet and avoidance of chilling are indicated Of course every effort should be made to clear up the carrier state of the throat by using penicillin therapy

CARDITIS and ARTHRITIS are best treated if one remembers that the complications of scarlet fever are part of the rheumatic fever syndrome and appropriate treatment for rheumatic fever is instituted promptly

Summary The treatment of choice for scarlet fever consists of the early recognition of the etiologic organism and treating it promptly with bed rest adequate diet and fluids and the prompt administration of penicillin for a minimum of 6 days preferably 10 days Aspirin is indicated as a blocking agent throughout the early part of the illness Prophylactic immunization is of little or no value

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RHEUMATIC FEVER AND CHOREA

In recent years the increase in medical knowledge has led to a holistic or totalistic concept of diseases Rheumatic fever is not a distinct disease entity From the etiologic standpoint rheumatic fever is a poststrepto coccal disease a nonsuppurative complica tion of an invasion by one or more of the subtypes of group A streptococci (Rantz et al) From the pathologic standpoint rheu matic fever is one of the great group of collag enous diseases (Rich and Gregory) It is believed that rheumatic fever results from an antigen (derived from the streptococcus) spreading with the help of enzymes and co enzymes (such as hyaluronic acid and hy aluronidase) into contiguous mesenchymal structures Since the arteries arterioles and capillaries are the contiguous structures rheumatic fever is characterized by arteritis Because the collagenous degeneration of the vessels may be abrupt the terms "anaphylac tic" or "hypersensitivity" are applied The multiple system manifestations result from the location of the involved vessels at a given time Thus chorea is clinical evidence of ac tive arteritis in the central nervous system as shown by Costero and associates carditis is evidence of arteritis in the myocardium peri cardium and endocardium pneumonitis is evidence of arteritis in the pulmonary ves sels and polyarthritis is evidence of arteritis in the synovial membranes of the joints

Aim of Treatment The aim of treatment of rheumatic fever therefore should be *five fold*

(1) To prevent streptococcal epidemics
(2) To terminate a streptococcal invasion in the nasopharynx quickly in order to lessen the amount of antigen ab sorbed into the circulating fluids
(3) To block the antigen which is absorbed from spreading into mesen chymal cells and prevent the collage nous degeneration
(4) To marshal all of the available thera peutic armamentarium so that little permanent damage results from the active inflammatory stage of the dis ease thus preventing crippling heart disease
(5) To teach the patient and family a way of life so that recurrent attacks will be prevented and the patient with serious heart disease can be a useful citizen in the community

These objectives are broad and perhaps idealistic but without them little will be accomplished in the prevention of crippling rheumatic heart disease

Prevention of Epidemics It is a known and accepted fact that rheumatic fever epi demics follow epidemics of streptococcal throat infections Paul Jones Rantz and many others have demonstrated this fact The most recent example is the experience of the Army in Japan and Korea in 1947 where epidemic streptococcal throat infec tions were followed by rheumatic fever in 29 per cent and 31 per cent of cases re spectively (Griffith) An epidemic applies to a home as well as to a community or an army Every case of streptococcal infection of the nasopharynx no matter what the clini cal manifestations are whether it is an acute nasopharyngitis a follicular tonsillitis or scarlet fever should be isolated in the home in a private room, or in an infectious ward Measures to prevent the spread of the in fection must be instituted such as the wear ing of face masks by all attendants washing

[illegible] each home is con sidered as a seedbed of an epidemic the spread of streptococcal epidemics will be lessened

Termination of the Infection The strep tococcal infection of the nasopharynx should be terminated as quickly as possible In this manner the amount of antigen absorbed is lessened specific type change of organisms will be prevented and the likelihood of an attack of rheumatic fever greatly reduced as shown by Massell

The ideal treatment of the acute strepto coccal sore throat is by penicillin either orally in 600 000 units daily or a similar dosage parenterally This treatment should be continued for 10 days to insure against

reactivation of the infection or an invasion

bodies are formed The use of sulfonamide drugs, such as sulfadiazine, is not as successful as penicillin (Hoyne and Brown Meads et al) and convalescent serum (Hirsh et al) Sulfonamide drugs tend to increase the tendency to the development of the collagenous complications Convalescent serum is attended with the danger of *serum sickness*, infectious hepatitis, or both

Therefore, the aim of treatment in every case of streptococcal invasion of the nasopharynx is quick termination of the infection in order to prevent poststreptococcal complications, such as rheumatic fever

Blocking Agents During the growth and reproduction of the streptococcal organisms in the throat, toxic substances are absorbed by the lymphatics in the nasopharynx *These substances are antigens* which circulate in the blood stream The spreading factor, of which the best known example is hyaluronidase causes these antigenic substances to penetrate the mesenchymal cells The first mesenchymal structures which the antigens contact are the arteries arterioles, [illegible]

degeneration of these structures be prevented *Normally the protective mechanism* of the body by antigen stimulation of antibody formation goes on unopposed, but in those patients where large amounts of antigen, enzymes and co enzymes of the spreading factor type are present nonsuppurative, inflammatory reactions in the mesenchymal tissue may occur It is important, therefore, to block the antigens from penetrating the *mesenchymal* cells Guera has demonstrated that tissues saturated with salicylic acid are not penetrated by *antigenic substances*, or at least the penetration is definitely delayed Kyser and his co workers have been able to show that animals which are well saturated with benadryl do not readily develop rheumatic-like lesions after receiving injections of a foreign substance, such as horse serum Knowing, therefore, that the salicylates prevent or slow down the spreading factor, it is logical to assume that giving large amounts of the salicylates at the *time of the streptococcal invasion* of the throat, and for 6 to 8 *days thereafter, will help* to block the penetration of the antigen into the mesenchymal cells, and thus prevent the development of poststreptococcal nonsuppurative complications, such as rheumatic fever It is believed that the older physician, who treated his patients with large doses of the salicylates during and following a streptococcal *throat* infection, did much to prevent the *development of rheumatic fever The best blocking* agent so far found is salicylic acid It is wise to give a patient with a streptococcal sore throat 1 grain of acetylsalicylic acid per pound of body weight per day until the patient has fully recovered from the throat infection and the danger of a poststreptococcal, inflammatory reaction, such as rheumatic fever, has passed

Available Therapeutic Armamentarium. Once rheumatic fever has developed, the *main objective of the physician is to terminate* the rheumatic fever as quickly as possible and, during the course of the rheumatic fever, prevent crippling heart damage, if possible Since there is no specific treatment for rheumatic fever, it is important that all available armamentaria be utilized to prevent prolonged morbidity and crippling heart disease It has become the theme of *public health agencies to emphasize* the dire effect of rheumatic fever Instead of implanting *fear of a fatal outcome or fear of crippling* heart disease in the minds of the patient and the family of the *patient, I believe* it is much more desirable that the physician point out that, with proper care much can be done to prevent the serious crippling heart disease which has been so greatly feared It is true that only 1 out of 2 children who develop rheumatic fever with heart disease live to the age of 40 It is known, however, that if a child has only one attack, and escapes serious heart damage, 90 per cent of the patients who reach the *age of 21 or more are able to carry* on normal activity without circulatory symptoms *Therefore, the aim of the physician* who recognizes the primary attack of rheumatic fever is to direct the care *of this patient* so as to prevent crippling heart disease during the primary attack, and thereafter to *prevent* recurrent attacks, since reactivation of rheu

matic fever most frequently causes serious crippling heart disease

The Treatment of Suspects Every patient with a hemolytic streptococcal sore throat is a potential rheumatic fever subject especially if he comes from a family with a rheumatic background or if he has had previous attacks of streptococcal throat infections It is imperative therefore that this patient be observed over a sufficiently long period to detect the onset of an active rheumatic state at the earliest possible moment A patient who is slow in recovering from the acute hemolytic streptococcal throat infection who is pale irritable nervous has a lessened span of attention and concentration runs a low grade fever and on study is found to have an elevated antistreptocolysin titer and perhaps an elevated sedimentation rate should be treated as a potential rheumatic fever patient As stated above the throat infection should be cleared as promptly as possible with the use of penicillin The patient should be given aspirin in the dosage of 1 grain per pound of body weight per day until the above mentioned symptoms and signs have subsided and until the physician is sure that carditis has not developed The patient who has developed rheumatic fever either of the fulminating or of the polycyclic or low grade continuous type should be placed on a therapeutic regimen modeled somewhat after the following plan

Rest Rest in bed is imperative for the patient with rheumatic fever throughout the entire stage of rheumatic activity In the acute fulminating type where there is high fever and red hot swollen joints together with evidence of myocardial involvement the patient should be kept quiet in bed Instructions to remain quiet are usually not necessary because the patient is so ill that he only moves on command He is restless sleepless and irritable but he does not move about physically in the bed However as soon as the patient becomes comfortable it is necessary to continue the bed rest and bed

means permission to sit up with a backrest and to feed one s self Quiet surroundings in the early stage are imperative so that sleep is readily induced Diversional facilities must be provided so that boredom and introspection are avoided As the pain and general discomfort subside rest must be judiciously proportioned to the stage of rheumatic activity Deep breathing exercises are instituted as soon as the patient is comfortable Follow

when these exercises can be accomplished without an increase in the heart rate flexion and extension exercises are increased to per

rest for the heart muscle and circulation is maintained It is believed that mild deep breathing exercises and moderate flexion and extension exercises of the extremities promote the circulation and lessen the burden on the heart rather than keeping the patient so absolutely quiet that the heart of necessity must do most of the work

Nursing Care Nursing care must be wisely and intelligently carried out Comfort rest sleep cleanliness and careful attention to diet and elimination are elementary but essential nursing services A daily tepid bath with change of linen an attractive diet and intestinal regulation do much to improve the patient s mental attitude toward the disease As soon as the patient is comfortable he should be permitted to do most of the body hygiene himself This does not mean that he is permitted out of bed to walk to the bathroom He is allowed to sit up in bed brush his teeth wash his hands and face and to enjoy his meals when such exercise does not bring on fatigue shortness of breath or increase in the heart rate The attitude of the nurse should be one of positive approach to health with a good mental attitude rather than a negative approach which constantly inhibits the patient and reminds him of possible danger to his heart

Diet The diet should be a highly nutritious one It should be so planned that the patient s nutrition will be well maintained [illegible]

vitamins This diet is best obtained by giving eggs meat fruit and green vegetables Milk

in moderate quantities should be provided Excess of sugars, starch, and sweet desserts should be avoided In the early stages of the illness, when the patient is running a high fever and is restless and uncomfortable, a liquid to a soft diet should be given, that will, however, maintain the caloric content The average child should receive a caloric content of 2500 to 3000 calories a day, while the young adult should receive at least 3500 calories daily The form of the diet is entirely dependent on the patient's condition and the stage of activity of the disease

Drugs There is no specific drug therapy in the treatment of rheumatic fever Various drugs have been used, such as aminopyrine colchicine, cinchona derivatives, calcium benzyl succinate, and many forms of the salicylates, as well as the newer drugs, such as the sulfonamides and penicillin All drugs have been disappointing in that they fail to attain the goal of the physician, that is to prevent crippling heart disease The salicylates are the only drugs which have survived the test of time Most clinicians agree that the salicylates have an analgesic and antipyretic action Coburn believed that the early administration of massive doses of the salicylates would prevent crippling heart disease This work has not been confirmed It is believed that the salicylates are helpful in the exudative phase of the disease Their sphere of greatest influence is in their action as a blocking agent, but once the disease is well established, they only modify the inflammatory process Fever is lowered, painful joints are relieved more rapidly with the use of the salicylates pain is alleviated, and transudates into the serous cavities are more quickly absorbed during their use However, they have no effect on terminating the disease process, and no proved effect in preventing heart damage Furthermore, the salicylates have less and less analgesic and antipyretic value in the second and third cycles of the [illegible] cases

permitted activity more readily than if the drug were not administered Salicylates do not prevent recrudescence of the disease, as seen in the polycyclic type of rheumatic fever The salicylates should be given in large dosage The best form of the salicylate is the acetylsalicylic acid salt, or plain a[spirin] The dosage is 1 grain per pound p[er] day, that is, the 30 lb child would rece[ive] 30 grains per day, a man weighing 150 lb would receive 150 grains per day in equal divided doses administered every 3 hour[s] It is not necessary to give the salicylat[e] intravenously Coburn has advocated an in[tra]travenous solution of 1000 cc of a 1 per ce[nt] sodium salicylate over a period of 10 hou[rs] to maintain a satisfactory blood level of [2]5 to 35 mg per 100 cc of blood The dosag[e] as mentioned above when given orally wi[ll] maintain this satisfactory blood level witho[ut] difficulty Therefore, the salicylates should b[e] given by mouth in the form of aspirin ever[y] 3 hours around the clock Aspirin is readil[y] absorbed from the stomach It appears i[n] the blood in 15 minutes and reaches it[s] highest level in approximately 3 hours It [is] rapidly eliminated and the blood level be[gins] to fall about the third hour period Therefore, if the dosage is given every [3] hours, a constant blood level of 25 to 35 mg per 100 cc can readily be maintained It i[s] not necessary to administer sodium bicarbonate with the salicylates Gastric irritation ca[n] be prevented if food is given with each dos[e] of the salicylate Salicylism can easily be prevented if a large amount of fluid is given with each dose of the salicylate It is requisite tha[t] at least 3000 cc of fluid be given daily to each patient who is on salicylate therapy In ou[r] experience, only those patients who wer[e] not taking an adequate amount of fluid developed salicylism Salicylism appears whenever the blood level climbs to 50 mg pe[r] 100 cc, or beyond this level Salicylism, characterized by burning of the eyes, headache nausea, sweating drowsiness, and hyperpnea can be relieved promptly by the administration of large quantities of fluid orally, often without withdrawal of the drug If the blood level is under 25 mg per 100 cc, it is easily deduced that the patient is not receiving a calculated dose of 1 grain per pound per day Since it is impossible to state when a patient with carditis will go either into right or left sided heart failure, it is unwise to give the patient sodium bicarbonate along with the salicylates Pulmonary edema and passive congestion of the liver are difficult to control if the patient has received large amounts of sodium in the form of sodium salicylate or

sodium bicarbonate Salicylates by rectum are ineffective since doubling the oral dosage raises the blood level to only 7 mg or less Acetylsalicylic acid orally in dosages of 1 grain per pound of body weight given in divided doses at 3 hour intervals with at least 3000 cc of fluid will maintain a satisfactory blood salicylate level of 25 to 50 mg For example a patient weighing 120 pounds should be given 120 grains of aspirin in 15 grain doses every 3 hours around the clock with 400 cc of water with each dose

Hench and his associates reported the effect of 17 hydroxy 11 dihydrocorticosterone (cortisone or compound E) on the acute phase of rheumatic fever stating that in 3 cases there was a rapid disappearance not only of the fever tachycardia and polyarthritis but also of the elevated sedimentation rates and abnormalities of the electrocardiogram The rationale for the administration of the compound E is based on the exhausted state of the adrenal cortex as shown by Selye The author has employed adrenal corticotropic hormone (ACTH) in an exceedingly acute fulminating rheumatic carditis with excellent laboratory evidence of improvement in adrenal cortical function and simultaneous drop in the fever tachycardia gallop rhythm leukocyte count and sedimentation rate It has not been shown as yet that the primary improvement in the rheumatic activity will be permanent nor has it been proved that their use will not be followed by other manifestations of endocrine dysfunction It is too early to be enthusiastic about this type of treatment but the outlook is hopeful

When cortisone (compound E) or ACTH is being administered the patient must be hospitalized and careful observations of the metabolic status carried out Blood sodium and not [illegible]

[illegible]

cates fluid retention and is a danger signal If ACTH is being used frequent eosinophil counts may act as a guide to dosage The specific dose of each drug will vary with the individual patient and depends on the response to treatment Both preparations are administered intramuscularly in divided doses If ACTH is used 60 to 100 mg daily may be tried With cortisone 80 to 100 mg daily is an average dose

Oxygen Oxygen is of great value in the treatment of rheumatic fever rheumatic pneumonitis and congestive heart failure The restlessness cyanosis tachycardia and dyspnea are relieved by the administration of oxygen Oxygen should be given early and as long as the patient requires its help It is best administered by the nasal tube method passing approximately 4 liters of oxygen per minute through a humidifier and into the nasopharynx By this method the coldness of the oxygen tent is avoided and the patient is less annoyed by feeding and nursing care

[illegible]

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administered unless there are signs of congestive heart failure Shortness of breath may be due to pneumonitis or to left sided failure Where there are shortness of breath and evidence of both right and left sided failure digitalis should be given a trial Digitalis glucoside the drug of choice in full dosage should be given over a period of 24 hours and then maintained until the effects are noted If digitoxin is used 0 1 mg per 10 pounds of body weight should be administered in three or four divided doses for the first day For example a boy weighing 120 lbs should receive 1 2 mg of digitoxin in 0 4 mg dosage every 4 hours for three doses He then should be continued on 0 1 mg daily

Frequently it is found that digitalis does not improve the heart failure and in the writer's experience it is then best to withdraw the drug entirely Premature beats paroxysmal auricular tachycardia and paroxysmal auricular fibrillation are rare in primary attacks of rheumatic fever They occur frequently where there is serious heart damage that is in second or third recurrences of rheumatic fever

Quinidine Quinidine is not helpful in controlling the attacks in the primary stages of rheumatic fever but may be useful where there is evidence of auricular enlargement as in mitral stenosis Rest oxygen and the avoidance of nicotine are of distinct value in preventing the arrhythmias during the acute carditis of rheumatic fever *Quinidine*

and related drugs are disappointing in their usefulness

Diuretics Diuretics are used when there is evidence of congestive heart failure In acute carditis the diuretics are of greater value than any other drug when congestive failure appears Especially is this true when right sided failure is primary Right sided failure is frequently primary owing to the associated rheumatic pneumonitis The diuretic of choice is a xanthine derivative by mouth or salyrgan mercupurin or mercuhydrin given intravenously or intramuscularly The preferable method is 1 cc of mercuhydrin intramuscularly every day to insure an output of two thirds of the intake Mercurial diuretics should not be used if there is evidence of acute glomerular nephritis

Sulfonamides The sulfa drugs have not proved useful in the treatment of rheumatic fever The drugs have been used in the treatment of rheumatic fever because of the apparent relationship between the streptococcal throat infections and the active rheumatic state Since the use of the sulfa drugs is inclined to increase the tendency to develop the collagenous degeneration of the arterioles it is wise not to use sulfa when rheumatic fever is established The use of sulfadiazine in 0 5 to 1 gm dosage daily in the quiescent period to prevent recurrent attacks of sore throat may prove wise however much study should be done on this subject and if there is any question of rheumatic activity the prophylactic use of the drug should be withheld

Penicillin Penicillin is not beneficial in the treatment of rheumatic fever It is definitely harmful when continued over a long period of time Penicillin should be used to clear up the streptococcal sore throat and the carrier state but should not be continued over a period of weeks and months As soon as the throat has been cleared of the invading streptococcal organism the penicillin should be withdrawn Intercurrent streptococcal infections of the nose and throat should be treated with penicillin orally or parenterally in dosage of 600 000 units daily

Vitamins If the rheumatic fever patient is consuming an adequate caloric diet high in proteins it is not necessary to add supplementary vitamins However if he is seriously ill and his dietary intake is deficient vitamins should be added Vitamin C has been disappointing in that it has not caused a more rapid convalescence It does tend to help level the temperature curve and the sedimentation rate Vitamin P hesperidin rutin vitamin K and calcium in large dos [illegible]

add a therapeutic dose of the vitamins when the dietary intake is unsatisfactory

Iron Ferrous sulfate in dosage of 3 to 6 grains three times a day is useful in correcting anemia secondary to the active rheumatic state

Fever Therapy Fever therapy has not been of value in terminating the active rheumatic state Chorea clears up rapidly with fever therapy either through the use of typhoid vaccine intravenously or through the use of the Kettering hypertherm However if the heart disease and other manifestations of the rheumatic state continue it is doubtful if fever therapy does more than give temporary relief from the nervous manifestations resulting from the involvement of the central nervous system

Roentgen Therapy Treatment through the myocardium in the treatment of the active phase of carditis or rheumatic fever has not proved of value in the hands of the author Levy and Golden from 1926 to 1935 were able to show that roentgen therapy was of value in terminating the active carditis

Foci of Infection The removal of foci of infection is not attempted in the active phase of the disease Tonsillectomy during the active phase of the disease resulted in a recrudescence of the rheumatic state in all cases in a series studied by the author Tonsillectomy was best carried out when the active stage had terminated at least 3 to 4 months previously The treatment of focal infection in the nasopharynx and tonsils by roentgen or radium therapy has been useful especially where the tonsils are obstructive because of their large size Dental surgery should be postponed until all signs of rheumatic activity have subsided for at least 3 to 4 months Blood plasma sera and vaccines have not been helpful in the

treatment of the active phase of rheumatic fever

Climatotherapy Exposure of the rheumatic fever patient to a warm dry climate and regulated heliotherapy is of some general benefit The virulence of the hemolytic streptococci may be less in a warm dry climate and the fulminating type of rheumatic fever is much less in such an environment However the incidence of heart disease resulting from rheumatic fever is not much more diminished in the warm dry climate than it is in the climate of the temperate zone In general it is believed that *recrudescence and reactivation of the disease are decreased in a warm dry climate and that heliotherapy is of general health promoting value However exposure to sun*shine must be gradual and well regulated as sunburn can reactivate the rheumatic state as promptly as a streptococcal infection

Physiotherapy Physiotherapy is definitely harmful in the exudative state of the rheumatic polyarthritis It is of some value in the older age group when there is residual muscle weakness jelling and arthralgia but treatment must be mild and not too vigorous

Avoidance of Infection Since there is a direct relationship between the degree of carditis and the frequency of reactivation of the rheumatic state infection must be avoided At the onset of an upper respiratory infection the rheumatic fever patient even though he is in the quiescent state should be put to rest *Isolation should be practiced* Throat cultures should be taken and if the patient has a positive throat culture penicillin *should be given orally to clear up the* infection and aspirin in large dosage should also be given to act as a blocking agent *With a recurrent upper respiratory infection of a streptococcal nature* care should be taken to find the carrier in the home or in the school and to treat him in order to eliminate such infection The daily administration of sulfathiazole or sulfadiazine throughout the year will reduce the incidence of streptococcal infection but the danger of sulfa sensitivity is marked and if sulfa drugs are used prophylactically the patient should be watched carefully for evidence of sulfa sensitivity The use of penicillin in a prophylactic program is largely inhibited because of the cost The same is *true for aureomycin at the present time* Since penicillin therapy for the acute hemolytic streptococcal infections of the throat is effective the occurrence of recrudescence and reactivation can be prevented by the early treatment of the streptococcal sore throat by penicillin

Convalescence EDUCATIONAL PROGRAM Every child or patient who is convalescing from rheumatic fever should continue with his school work Most cities and rural districts provide a home school teacher and the patient should be encouraged to follow the school program diligently

OCCUPATIONAL THERAPY Occupational therapy is of utmost value In the early phases of the disease when the patient is *recovering from the acute illness diversional*

the training for a trade are advisable Watch making photography lathe work plastics and ceramics all make useful fields for the training of the hands while the child or young adult is at rest in bed In this manner cardiac invalidism is minimized in the pa

have an occupation whereby he can become a useful citizen and support himself in the community without throwing a burden on his heart by undue physical activity

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ERYSIPELAS

Erysipelas is usually not a primary disease It tends to follow skin diseases of pyogenic character, such as furuncles, infectious wounds, eczemas, impetigo chronic otitis media, herpes zoster, and conjunctivitis Erysipelas tends to occur most frequently in the older age group Sixty per cent of all cases occur between the ages of 30 and 70 Of 260 *cases* studied by Charosky, 213 *cases* occurred on the face, 42 on the legs, with less frequent occurrences on the trunk, arms and genitalia

The aim of treatment should be prevention All skin infections particularly suppurative infections, should be cleared up as rapidly as possible Chronic infections should not be scratched or in any other manner contaminated Erysipelas which has once become established should be treated promptly There are two treatments of choice (1) 25 per cent sulfadiazine ointment applied generously to the infected area at frequent intervals (2) penicillin by intramuscular injection in a dose of 25 000 to 50 000 units every 3 hours for 48 to 96 hours 300 000 units given intramuscularly once a day is also a satisfactory form of treatment A combination of the local application of sulfa ointment and penicillin may be desirable in severe cases The general treatment consists of rest, a well balanced highly nourishing diet forcing of fluids up to 3000 cc a day, provided there is no evidence of heart failure, and good elimination by attention to intestinal regularity The older methods of treatment, such as painting the edges of the lesion with iodine, magnesium sulfate packs, and ultraviolet or roentgen irradiation have been supplanted by the use of the sulfadiazine ointment or the intramuscular use of penicillin

GEORGE C GRIFFITH

GONORRHEA

Before proceeding with the treatment of gonorrhea, it would be well to establish the diagnosis All too frequently a nonspecific urethritis is considered to be of gonorrheal origin A careful history as to exposure and estimation of the incubation period as to the onset of symptoms are of value The great majority of gonorrheal infections occur within 2 to 9 days after exposure

The most important diagnostic feature is

which will ferment glucose The use of complement fixation tests is of some value especially in the metastatic lesions due to gonococci, such as arthritis, where the test is *apt to be positive In acute gonorrhea* and in chronic gonorrhea which tends to remain localized at its point of origin, i e the urethra, the complement fixation test may be of no value

Prophylaxis The prevention of gonorrhea is primarily a public health problem and education of the young adult population is the important task There has been too much reticence on the part of the doctor and the patient in the discussion of this important disease Many reputable physicians dislike to care for patients suffering from gonorrhea because of the social nature of the problem Any doctor who does not know and willingly give advice and treatment to these patients is unmindful of the possible terrible devastation of this disease

In the armed services the most recent attempt at prophylaxis has been the routine administration of penicillin orally (500 000 units) to all enlisted personnel returning from leave This has resulted in a significant reduction in the incidence of gonorrhea, but has not completely prevented *all cases.* It

would seem both possible and practical to give all patients who have been exposed oral penicillin in daily doses of 500,000 units for 3 days, or, one injection of 300,000 units of penicillin intramuscularly

Active Treatment GONOCOCCAL URETHRITIS When the diagnosis has been estab lished, penicillin is the drug of choice It is important to inspect the urethra and genitalia thoroughly for suspicious lesions, and darkfield examination should be done before any penicillin is given Penicillin has been known to mask the presence of syphilis in persons having gonorrhea Therefore, it should be routine for all patients suffering from gonorrhea who are treated with peni cillin to have a Kahn test taken at monthly intervals for at least 3 months following the cure of the gonorrhea

Many opinions exist as to the preparation dosage, and method of administration of penicillin At the present time the single dose of 300 000 units of penicillin injected intra muscularly in the gluteal region is most popular This should be augmented with a sulfa drug, either sulfadiazine or sulfathiazole in 1 gm doses, three times a day While alkalinization is not essential, bicarbonate of soda in 0 6 gm dosage is best given along with the sulfa

In most cases so treated, the urethral dis charge disappears within the first 24 hours However, the urine will still contain shreds and pus cells owing to the fact that the ulcerations caused by the gonococci do not heal [illegible] time the sulfa and soda are continued A negative smear of the urethra or stained urine sediment for 3 successive days is a [illegible]

[illegible] istence of such acquired resistance There is no question that some patients are not cured by penicillin and sulfa preparations This may be due to inaccessible organisms in the prostate, seminal vesicles, or urethral glands by which the patient becomes reinfected when the concentration of the drug (either penicillin or sulfa) disappears Some of the so-called resistant cases may be patients who have acquired a nonspecific urethritis along with their gonorrheal infection, or who may have had a pre existing urethritis or prostatitis

Provocative tests as criteria for cures are to be condemned, the passage of sounds, and the injection of silver nitrate solutions into a recently infected urethra are of no benefit to the patient

While the patient is under treatment, it is well for him to avoid alcohol, highly spiced foods, and sexual excitement

Cure of acute gonorrhea has been effected in from 90 to 100 per cent of all cases with the single injection method of penicillin Of those not cured by a single injection, the majority are cured by a second injection Because of the excellent results in the treatment of acute gonorrhea, the incidence of complications has been markedly reduced It is a well known fact that complications are rare in acute anterior urethritis but fairly com mon in posterior urethritis

Posterior urethritis occurs approximately 4 to 6 weeks following the acute anterior urethritis It is manifested by marked frequency of urination, with tenderness and occasionally some terminal hematuria There may be constitutional symptoms such as malaise, mild headache and feeling of fullness in the perineum Fever may be present with leukocytosis

When posterior urethritis occurs, the patient should be put to bed, and fluids forced to 2500 to 3000 cc daily An alkaline diuretic, composed of tr hyoscyamus 10 cc, potassium citrate 10 gm in 3 oz of a suitable vehicle, is prescribed A teaspoonful three times daily allays the urethral symptoms If pain is troublesome and the patient is rest less, a rectal suppository containing powdered opium, 0 060 gm and extract of belladonna 0 015 gm every 4 to 5 hours gives marked relief

It is well during the course of posterior urethritis to continue penicillin in doses of 20,000 units every 4 hours intramuscularly If the sulfa drugs are continued beyond the [illegible] ministered

It is important to cure the posterior ure-

thritis because this is the focus from which the more serious complications develop such as arthritis endocarditis and local extension of the disease as epididymitis orchitis seminal vesiculitis and prostatitis

EPIDIDYMITIS Acute unilateral or bilateral epididymitis does not respond as quickly to penicillin treatment as does the acute gonococcal urethritis This may be due to the poor drainage of the epididymis Hence large doses and more prolonged treatment may be required The testicles should be elevated and constantly immobilized This is best accomplished by a snug fitting suspensory which has leg straps The use of cold compresses or a covered ice bag is useful early in epididymitis to minimize swelling after the first 48 hours heat gives relief from pain Codeine 0 060 gm and aspirin 0 3 gm given in capsule form every 4 to 5 hours are also helpful in relieving pain Most cases of epididymitis tend to cure themselves spontaneously in 4 to 5 weeks the swelling disappears so that only a small area of scar tissue remains in the globus major of the epididymis Operation is indicated only when the swelling persists and definite fluctuation is present In a high percentage of cases of bilateral epididymitis sterility due to aspermia in the ejaculate occurs

PROSTATITIS Prostatitis due to gonorrhea usually responds to large doses of and prolonged treatment with penicillin With the patient at rest 20 000 units of penicillin in aqueous solution every 3 hours are given until clinical results are noted It is not advisable to massage the prostate in order to make a culture until at least one week has elapsed following clinical cure It is well known that in gonococcal prostatitis other organisms notably staphylococcus and streptococcus intervene and may give rise to a nonspecific chronic prostatitis

SALPINGITIS Penicillin is effective in salpingitis and pelvic cellulitis before abscess formation intervenes Treatment should be continued until a smear from the urethra cervix and vagina are negative Where symptoms persist despite negative smears surgery may be ultimately indicated for removal or drainage of chronic pyosalpinx or hydrosalpinx Penicillin has been helpful in postoperative management

VULVOVAGINITIS IN CHILDREN Penicillin is effective here Doses should be approximately 1000 units per 5 lbs of body weight every 3 hours in very young children In older children somewhat larger doses approximately 100 000 to 200 000 units daily are given fractionally every 3 hours Criteria of the cure will be cessation of the signs and symptoms of infection and negative smears for 3 successive days Segregation of the patient from other children and aseptic precautions should be taken to prevent spread of the infection to others

OPHTHALMIA NEONATORUM The use of 1 per cent silver nitrate prophylactically in all newborn infants is still a sound principle and should not be abandoned despite an occasional chemical conjunctivitis If gonorrheal ophthalmia occurs the infant should receive 500 units of penicillin per pound of body weight intramuscularly every 3 hours In addition penicillin in saline solution containing 1000 to 2500 units per cubic centimeter should be used locally This should be instilled every 2 to 3 hours during the day In conjunctivitis with profuse discharge more frequent irrigations are indicated Treatments are indicated until signs and symptoms subside and smears are constantly negative for 3 successive days

PROCTITIS While gonorrheal proctitis is uncommon it responds well to penicillin therapy In severe cases the use of larger doses for a prolonged period of time may be necessary

ARTHRITIS This is perhaps the most common of metastatic gonococcal complications occurring in about 3 per cent of gonorrheal infections The knee ankle elbow or wrist is attacked the frequency being in this order It is usually polyarticular and occurs within 1 to 4 weeks following the primary infection Sulfathiazole and sulfapyridine are effective in acute gonorrheal arthritis but in chronic cases may not be as effective Penicillin may be effective in some cases In acute arthritis 40 000 units every 3 hours usually effect a cure within 3 days In chronic gonorrheal arthritis the same plan of treatment may be prolonged Fever therapy is also helpful in chronic arthritis and is combined with penicillin therapy It is unwise to attempt local treatment of a primary lesion

such as prostatitis by massage, because of the danger of the exacerbations of the arthritis

Immobilization of the joint and heat help to reduce the pain Aspiration of the fluid from the joint space is an aid to diagnosis [illegible] and surgical [illegible] cases

JAMES I FARRELL

CHANCROID INFECTION

Sulfathiazole is effective in this infection An initial dose of 2 gm is given followed by 1 gm every 4 hours for 7 days Incision and drainage of fluctuant adenitis are advisable Dusting of the lesions with sulfanilamide is likewise beneficial Local treatment should be confined to cleansing moist dressings of 1 8000 potassium permanganate solution In phimosis a dorsal slit may be necessary for exposure and cleansing of the lesions It is wise to do several darkfield examinations as syphilis may be a concomitant infection

JAMES I FARRELL

BRUCELLOSIS

Human brucellosis, commonly known as undulant fever, may be defined as a febrile disease characterized by morning remissions and irregular exacerbations of a multiple of other symptoms and signs The causative organism may be either *Brucella melitensis*, *Brucella abortus*, or *Brucella suis* The disease may take the form of a bacteremia or a focal infection

It is now a well established fact that brucellosis is an animal borne disease and that humans acquire infection from contact with infected animals or through the ingestion of infective animal foods

The duration of brucellosis is known to vary from 7 days to several years The variability in its duration often makes it difficult for the physician to interpret the value of specific agents that are used in treatment

The peculiar behavior of the organism within the host may also account for the poor response of the patient to various therapeutic agents It has been known since the early studies of Bang that Brucella organisms invade and multiply within many types of fixed tissue cells Bang's original findings recently have been elaborated on by the work of Castaneda who succeeded in demonstrating large numbers of Brucella organisms in many types of tissue cells of mice following experimental inoculation Large numbers of organisms were seen within macrophages, fibroblasts endothelial and reticular cells interstitial cells of the testes, and alveolar cells It is possible that the intermittent release of bacteria from tissue cells and invasion of new cells is responsible for the wave like form of temperature that characterizes the disease

The mortality rate in human brucellosis in the United States is still low, but if the organisms continue to increase in virulence as much as they have in recent years, there is the possibility that the disease will take a more severe course in the future and that the death rate will be higher

A large percentage of cases of the acute form of brucellosis, if recognized within 10 days after the onset and given bed rest and symptomatic treatment will recover from the disease within 6 to 8 weeks without specific treatment A wide variety of agents has been used for specific treatment Most of them have been discarded as worthless Brucella bacterins prepared in various forms have been used in the treatment of the disease for more than 30 years It is the opinion of many physicians who have had considerable experience with brucellosis that bacterins have not proved to be satisfactory therapeutic agents

Castaneda and Carrillo Cardenas have reported the treatment of 35 cases of melitensis brucellosis with a soluble antigen derived from crushed bacterial cells It is called "MPB" The average duration of symptoms in 35 cases before treatment was 10 months After treatment the average duration of symptoms was 3 2 months

For more than 15 years the writer and his associates produced and distributed for the treatment of brucellosis a bacterial filtrate known as "Brucellin" While this agent has served to shorten the duration of symptoms in many acute cases, it is doubtful whether it falls into the category of the kind that is most desired to effect a prompt and speedy cure of the disease

The reported results from the use of

chemotherapeutic agents such as the sulfonamides in the treatment of human brucellosis are conflicting and confusing Apparent recovery has been obtained from their use in certain cases but these were an exception rather than the rule

Recently one of the sulfonamides, sulfadiazine, has received new impetus as a therapeutic agent when administered simultaneously with streptomycin * Eisele and McCullough have reported complete cures in 2 acute cases with this form of therapy Spink and associates have obtained complete recoveries in 17 cases with a similar combination of agents For the average acute case, they recommend the intramuscular injection of 0 5 gm of streptomycin every 6 hours for 2 weeks with an initial oral administration of 4 gm of sulfadiazine and then 1 gm every 4 hours for at least 2 or 3 weeks

During the past 3 years, the writer has accumulated considerable data from in vitro and in vivo studies which show that rapid and complete termination of brucellosis in either experimentally infected guinea pigs or naturally acquired cases in human beings can be accomplished by making use of the potentiating property of certain of the sulfonamides on the serum antibody complement system

It has been found from in vitro and in vivo studies that normal blood serum or plasma will convert the bacteriostatic action of sulfadiazine to a bactericidal action The latter action depends on a combination of the drug, normal antibodies, and complement A bactericidal action was not obtained in the test tube or in the body of an infected animal by means of the drug in the presence of complement unless normal serum or plasma was added to test tube dilutions of the reagents concerned or was injected intravenously (In in vivo studies, complement was furnished by the infected animal)

The curative action of this type of therapy in human brucellosis depends upon maintaining, for a sufficient length of time, a low level (1 to 3 mg per cent) of sulfadiazine in the blood, the presence of sufficient normal antibodies in the donor blood used in the intravenous transfusion, and complement in the blood of the patient While a marked improvement in the condition of the patient may occur within 48 to 72 hours after the blood transfusion, complete destruction of all Brucella organisms present in the tissues of the patient may necessitate the combined presence of the three agents for 7 to 15 days

The procedure which this laboratory has recommended and which many physicians h [illegible]
c [illegible]
1 [illegible]
([illegible]
children) at 4 hour intervals for 24 hours At the end of the first 24 hour period, give one transfusion of either normal plasma (2 cc. per pound of body weight) or normal whole blood (3 cc per pound of body weight)

The administration of sulfadiazine should be continued at the same dosage and time interval for 7 days after the transfusion In certain cases, it is advisable to continue the drug for an additional 5 days, giving 7.5 grams twice daily at intervals of 12 hours

If there is no improvement or only a slight improvement in the condition of the patient within 4 days after the blood transfusion, a second one should be given

A few physicians, who have used the sulfadiazine-blood transfusion treatment in patients that had been injected previously with Brucella antigenic agents (bacterins or culture filtrates) have observed an enhancement of symptoms for 48 to 72 hours after the transfusion The patients became free from symptoms after the reaction

Recently Holmes and Hughes reported that they obtained complete cures in 2 cases of *Br. abortus* infection in humans in Eng

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* Spink and his co workers feel that aureomycin is as efficient as a combination of sulfadiazine and streptomycin in treating undulant fever These authors recommend the following dosage of aureomycin in acute cases

0 1 gm	in four divided doses on the	first day
0 6	" " " " " "	second day
1 6	" " " " " "	third day
2 0	" " " " "	from the fourth to the 10th day

[illegible] reported 4 cases of acute [illegible] combination [illegible] The aureomycin was administered every [illegible] hours in a dosage of 750 mg per dose One gm of dihydrostreptomycin was injected twice daily at 8 A.M and 8 P M — *Editor*

land through the use of sulfadiazine and blood transfusion therapy

General Treatment The patient should remain in bed during the acute stage of the disease and during specific treatment After the temperature has returned to normal complete rest should continue for another 15 days Noise and excitement should be avoided As much food should be given as can be assimilated A warm cleansing bath should be given each morning Constipation should be corrected with mild laxatives headache by the use of an ice cap or cold packs Nervousness and apprehensiveness may be allayed by bromides or phenobarbital in small doses Arthritic pains may be reduced by hot applications or radiant heat Anemia should be corrected with iron Ascorbic acid in daily doses of 200 to 500 mg is indicated in all forms of brucellosis

Most patients show a low basal metabolic rate This should be corrected by the administration of thyroid extract The adminis [illegible] is re [illegible]mmended [illegible]

[illegible] exertion and too much exercise

Preventive Measures No one who has worked for any length of time with brucellosis would suggest that there is some simple solution to the problem of its prevention In preventing a disease of this nature in humans one may make use of two well known and workable methods One involves the detection and slaughter of all infected animals the other the control of the avenues by which humans become infected from animals The animal slaughter method of attack should be used wherever practical The control of the avenues of infection involves the pasteurization of all milk from animals used for human consumption and avoidance of contact with infected animals and raw meat products from such animals

I Forest Huddleson

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TULAREMIA

Streptomycin is by universal agreement, the currently preferred agent for the treatment of tularemia (Keefer and Hewitt) * Its effects are so superior to those of specific antiserum that it has superseded serum ther [illegible]

therapy administered to desperately ill patients by so many individual physicians has resulted in such a low case fatality rate

General Therapy Bed rest is enforced during the acute febrile period and during the period of administration of therapy at any stage The initial diet should be appropriate for the initial clinical status and the nature and quantity of food offered thereafter are largely a matter of appetite taste and rapidity of convalescence Sitting up sitting

* Recently Woodward has indicated that aureomycin may be of more value in the treatment of tularemia than streptomycin An initial dose of 1 gm followed by 0.5 gm every 4 hours resulted in a normal temperature in 2 5 days after the beginning of treatment Further observations are necessary before this drug can adequately be evaluated

out of bed, and ambulatory status are each allowed as soon as return of ability and strength permits The resumption of work that requires considerable muscular activity is best postponed for at least 2 weeks after *fairly good physical competence* has been restored Relapses in tularemia are infrequent but are perhaps more prone to occur following physical exertion soon after spontaneous or induced recoveries (Berson and Harwell) *It is worth remembering* that there is as yet no evidence that streptomycin has ever killed all of the infecting bacteria in any tularemia patient or in any experimentally infected animal The available evidence is all to the contrary (Chapman et al) Hence the crucial event that mediates and conditions recovery is the transfer from a *bacteriostatic host dominance over the patient's* residual bacteria which is dependent upon the presence of streptomycin to one that is maintained solely by the host's natural defense apparatus This necessary process of transfer can be accomplished within 36 hours by the nonresistant mouse, but it appears to require a minimum of 4 to 5 days for most treated patients It is known for both animals and man that this host dominant *equilibrium can be upset by overexertion*, with consequent endogenous reinfection and clinical relapse The risk of post therapeutic relapse is greater if therapy is administered for only 1 to 3 days and it is *still greater* if this too brief treatment period should fall within the first 8 days of the disease It is difficult to interpret accumulating clinical experience otherwise than that the more severe or prolonged, or both the reaction of the patient to the infection prior to the administration of therapy the less the likelihood of relapse

Accessory or Special Therapy *Illnesses* of great severity are favorably modified so quickly that most of the former accessory or symptomatic measures are no longer needed With the notable exception of the buboes [illegible] infection re[illegible]tic alone [illegible]h is useful [illegible] a day or [illegible]ld be removed for physiologic reasons, they are seldom infectious beyond the third day of treatment Oxygen administration is advisable for a day or two if cyanosis is considerable in the stuporous pneumonic patient who also needs careful watching and preventive measures directed against the development of bed sores The infrequent patient *with* enteric infection and intense diarrhea may need parenteral fluids and salts Moist or dry heat will often ease the pain of large buboes and incision and drainage are necessary for those that suppurate, incision *preferably being delayed until liquefaction* is well advanced Ulcerated primary lesions are occasionally secondarily infected with pyogenic bacteria The mixed infections contribute somewhat to an increased incidence of *suppurative lymphadenitis and are there*fore of sufficient importance at times to warrant penicillin or other appropriate special *therapy, as well as magnesium sulfate* or other suitable wet dressings locally The indications are visible ascending lymphangitis, which is never produced by a pure tularemic infection, continued low grade fever, and buboes that recede much less than is usual under streptomycin therapy No primary lesion should be incised except to drain abscesses caused by secondary infecting agents

*Streptomycin Therapy The administra*tion of streptomycin should be started as soon as the diagnosis is made Deaths from fulminant infections, between the fourth and 10th days of the disease, will not be prevented if precious time is lost in futile efforts to get laboratory confirmation of the diagnosis which must be made solely on epidemiologic and clinical grounds *for patients* who become desperately ill during the first few days of the disease Since the earliest possible administration of streptomycin will not prevent the development of specific *serum agglutinins, the diagnosis* can always be verified after recovery has been achieved Although the maximal reduction in the duration of the disease and *disability is se*cured by the earliest treatment, streptomycin is highly effective in terminating disability as late as the fourth or fifth month of continuous, febrile disease

Dosage *Although there is* still insufficient experience to allow formulation of an average optimal dosage there has appeared no evidence that a total amount of 2 or 3 gm per patient, administered as 0 5 gm per day

for 2 days followed by 0 25 gm per day for 4 days or as 0 5 gm per day for 6 days is not adequate for most patients even those with infections of greater than average se verity There is no evidence yet that dosage in excess of 1 gm per day is a necessary requirement or that any total dose greater than 6 gm per patient has actually met a clinical indication that could not have been met adequately with 6 gm or less Desper ately ill patients may need 1 gm or more per day and it may be more effective in the stuporous patient if the first day s quota is administered as a continuous subcutaneous drip rather than by intermittent injections Frequent observations of changes in the psychic state and the temperature curve form the best clinical guides to quantity and frequency of dosage

Route and Frequency of Administra tion All ordinary indications are satisfied by intermittent intramuscular injections of the selected daily dose in three equal por tions at 8 hour intervals Many patients do extremely well if half of the daily intake is injected at 12 hour intervals It is unnecessary for the great majority of patients to use a 3 or 4 hour injection schedule The existing meager experience suggests that intrathecal administration is not necessary for satisfac tory treatment of tularemic meningitis

Duration of Administration It is far better to administer moderate doses over a 6 to 8 day period than to give larger amounts for a shorter time Acute relapses do not oc cur if the administration period covers a minimum of 5 or 6 days It is unwise to attempt 3 or 4 day treatments good re missions may be induced but relapses will occur and it then becomes necessary to do in two sessions what should have been done the first time

The Herxheimer Type of Reaction Whenever large pulmonary or serosal exu dates are present at the onset of therapy, the analogue of the Herxheimer reaction should be anticipated and if it occurs differentiated from a relapse This reaction a consequence of accelerated phagocytosis and solubiliza tion of bacterial bodies with intravascular flooding of antigenic substances owing to the high degree of effectiveness of strepto mycin therapy usually appears only in the sickest patients It is apt to occur about 1

malaise and perhaps dullness or even drow siness—all of variable intensity and duration depending to some extent on the dosage used and the size of the exudates and usually persisting for 6 to 14 days It is ac companied by a transitory *fall* in the ag glutinin titer the level rising again spontaneously as the fever subsides These reactions usually terminate at about the time that resolution of pulmonary exudates can first be detected unlike a relapse they cannot be modified in any way by additional streptomycin therapy Until now there is no record of the occurrence of a relapse after therapy at any effective dosage level if the duration of treatment was 5 or more days Several examples of this reaction have been reported (Cohen and Lasser, Foshay)

Suppuration of Buboes after General Recovery Although the dosages recom mended are sufficient for most patients with tularemic pneumonia the frequency of sup purative lymphadenitis will probably not be reduced by more than 50 per cent Much more streptomycin is needed to prevent liquefaction of some buboes than is required to prevent death from extensive tularemic pneumonia A choice apparently lies between higher dosage with a lower frequency of suppuration at an increased risk of impair ment of hearing or equilibrium or being satisfied with a 50 per cent reduction in sup puration with minimal risk to the eighth nerve Since early massive dosage has not prevented all suppuration the latter alterna tive seems preferable

Toxic Drug Reactions The most cogent reason for administering only enough strep tomycin to meet the clinical requirements especially in a disease with a low mortality rate of 7 4 per cent (Francis), is the well

tration of 1 2 gm daily for a total of 9 3 gm about three times the average amount now recommended has resulted in 25 months of partial disability in a former tularemic pa

tient owing to residual vertigo Transitory headache nausea, muscle cramps and general malaise as well as drug fever and tinnitus have occurred following as little as 0 5 gm at rates of 1 gm or less per day Vertigo and deafness are the after effects most to be feared In general the smaller the total dosage, the greater the likelihood that these consequences will be transitory or avoided entirely

Effect of Treatment on Immunity after Recovery All evidence presented hitherto indicates that the earliest possible *effective treatment does not interfere with* the development of the usual high degree of resistance to subsequent external re exposure that is characteristic of recovered immune cases

Streptomycin Resistance. In the American clinical experience of more than 20 000 reported cases man to man transfer of tularemia has been so rare and so dependent on gross and easily preventable accidents that one may consider every human infection as a blind alley so far as the future outlook for the infecting bacteria is concerned There is *no reason for present concern about the* public health consequences of the acquisition of streptomycin resistance by *Bacterium tularense*

Lee Foshay

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DIPHTHERIA

Preventive Treatment Active Immunization Active immunity is usually *conferred* by the administration of three doses of fluid or alum precipitated toxoid alone combined with tetanus toxoid, or with tetanus toxoid and pertussis vaccine For the most lasting protection alum precipitated antigen should be injected at monthly or bimonthly intervals at any age after the sixth month of life Should earlier immunization be desirable four monthly doses of the alum precipitated antigen are recommended and the Schick test should be performed 3 or 4 months after the last dose, to determine whether adequate immunity has been conferred For sustained immunity, some authorities recommend a *stimulating (reinforcing or booster) dose*

better sustained and a stimulating dose is recommended only before entrance into kindergarten or when intimate exposure is *likely to have occurred*

Procedure after Exposure Whenever a previously immunized child has been exposed to clinical diphtheria a Schick test should be performed and throat and nose cultures should be made If all of these tests are negative nothing further is necessary if the Schick test is positive and the cultures negative, a stimulating dose of toxoid should be administered promptly, if the *Schick test and cultures are positive* without clinical symptoms, a daily dose of penicillin (300 000 units) should be administered in *alternate lateral gluteal areas for several* days Only if clinical symptoms of diphtheria arise should antitoxin be used Immunity after recovery from clinical diphtheria as after administration of toxoid *usually persists* for years, but it is not always permanent Conversely, some individuals are immune without having had either the disease or preventive toxoid

After intimate exposure of a nonimmunized person a Schick test should be performed and throat cultures made promptly *If the* test is positive and the cultures are negative three doses of diphtheria toxoid should be *administered at 3 week intervals and ex*

posure should be avoided until active immunity has been established (negative Schick test) If the cultures are positive and the Schick test is negative the patient should be examined daily for clinical evidence of the disease Nothing should be done except spraying of the throat with penicillin solution (10 000 units per cubic centimeter) 6 to 8 times daily If cultures remain positive a dose of penicillin (300 000 units) should be administered in alternate lateral gluteal areas for 3 days Administration of diphtheria antitoxin should be reserved for clinical cases or when the Schick test and cultures remain positive after penicillin

Passive Immunization The decrease in diphtheria morbidity and mortality in recent years and the ability to immunize younger infants adequately with four monthly doses of alum precipitated antigen have made the prenatal injection of expectant mothers by obstetricians an unnecessary procedure

Schick Test The Schick test is best performed with a 1 cc dry sterile insulin or tuberculin syringe (graduated in 0 1 cc) and a 27 gauge needle After the inner surface of the left forearm has been cleansed with 70 per cent ethyl alcohol and dried 0 1 cc of the Schick test solution is injected intracutaneously *The best time to make the reading is 72 hours later* In the immune no local reaction is seen in the nonimmune a local area of hyperemia develops (15 mm or more in diameter) In the immune the diphtheria antitoxin level is at least 0 01 unit per cubic centimeter of serum A negative test in the newborn is presumed to indicate that adequate antitoxin has been transmitted through the placenta Both mother and infant show the same kind of reaction—both are either *immune or susceptible In the infant however* such immunity is passive i e transient and is usually lost after the first few months

Superiority of Alum precipitated Antigen The most satisfactory time interval between doses is 1 or 2 months Many infant welfare clinics and private physicians therefore prefer to administer prophylactic doses of antigens at the time of routine visits

should be avoided and the vial should be returned promptly to the refrigerator after the required dose has been removed The superior immunity response after alum precipitated antigen is apparently based on the delay in its elimination from the body whereby prolonged opportunity for the elaboration of specific antibodies occurs However the earlier in life active immunization is attempted the poorer the immunity response Therefore infants less than 6 months of age require four monthly doses of slow absorbing antigen

Administration of Alum precipitated Antigens The injection is best made into the deep subcutaneous tissues of alternate lateral gluteal areas To reduce the possibility of cyst formation to a minimum it is customary to terminate each dose with 0 1 cc of air which is followed promptly by light massage over the injection site Subsequent doses should never be administered in sites previously used Occurrence of a febrile or local reaction is rarely a contraindication for subsequent doses

Combined and Multiple Antigens Active immunity may be induced by the use of a single combined or multiple antigen Because diphtheria prevention has long been a well established routine procedure in private *practice and in infant welfare clinics* tetanus and pertussis immunizations have come to be given with it At first fluid mixtures of diphtheria and tetanus toxoids were used then alum precipitated In recent years the alum precipitated and aluminum hydroxide adsorbed multiple antigens of diphtheria and tetanus toxoids and pertussis vaccine have come rapidly into extensive use The most recent trend is to begin four

exist In 1943 Lapin wrote "The whole subject of mixed immunization requires a long follow up period to determine which antigen retains antigenicity for a long time" Since then numerous favorable reports have appeared on the use of combined and multiple antigens In this connection the Council on Pharmacy and Chemistry of the American Medical Association recently issued the lowing warning "Pending more

knowledge it is suggested that the user be guided by the dosage recommendation given on the manufacturer's product since this represents the dosage accepted by the investigators whose methods have been used in preparing the vaccine Triple antigen or D T P as alum precipitated diphtheria and tetanus toxoids and pertussis vaccine are now commonly called has rapidly become popular because active immunity can be conferred simultaneously against three diseases and fewer injections are needed Furthermore slow absorbing (alum precipitated) antigen has been concentrated into a small volume much time is spared for the physician and the parents and the patient's discomfort is minimized

REACTIONS The reaction after a dose of triple antigen (D T P) is seldom more severe than when each of the antigens is administered singly A systemic reaction is usually manifested by a transient fever A local reaction is either an indurated nodule or less frequently a fluctuating cyst which occasionally drains Should high fever follow a dose the amount of food should be reduced the drinking of water urged and several small doses of aspirin given for a day or two In a series of over 4 000 doses of D T P it was not necessary to subdivide or delay a dose on account of the severity of systemic or local reactions Contraindications for the administration of antigen are any acute febrile disease skin infection prematurity delay in physical or mental development or any tendency to convulsions During the 5 years since D T P has been used by the writer no infant or child is known to have developed convulsions after its administration

STIMULATING (REINFORCING BOOSTER ETC) DOSES Basic or primary immunity induced by the administration of diphtheria toxoid singly or combined with tetanus toxoid and pertussis vaccine is usually quantitative Its duration depends in great measure on the potency and dosage of the antigen the age of the patient the time interval between doses and number of doses A famous immunologist has said "The initial injections constitute the first half of active immunization secondary stimulation completes it" This so called secondary stimulation may result from subclinical exposure to the disease or from a single (booster) dose of antigen

SCHEDULE OF IMMUNIZATIONS

Age	*Antigen*
6 months *	D T P (*alum pptd*)
7 months	D T P (alum pptd)
8 months	D T P (alum pptd)
9 to 12 months	Smallpox vaccination
2 to 3 years	D T P (alum pptd)
(before nursery school)	Booster dose
5 to 6 years (before school)	D T P (alum pptd) Booster dose and smallpox revaccination
After known exposure of previously immunized	D T P (fluid or alum pptd) booster dose (promptly)

* If attempted earlier start at 3 or 4 months D T P (alum pptd) 4 monthly doses

Prophylactic Care of Patient The patient with clinical diphtheria should be isolated promptly whenever possible he is to be transferred to a contagious disease hospital where he should remain until at least two successive negative nose and throat cultures are reported If the patient remains at home adequate isolation and precautions are all important Contacts such as nonimmune children and adults should be quarantined until their cultures are negative Any member of the household or classroom with a positive culture should be examined every day or two and promptly Schick tested to ascertain immunity or susceptibility When exposed susceptibles have not been actively immunized and cannot be examined daily a prophylactic dose (*5000 units*) of antitoxin may be necessary

Active Treatment SPECIFIC An ample initial dose of diphtheria antitoxin should be administered as early as possible Only antitoxin that has been kept properly refrigerated and that is not outdated should be used Antitoxin neutralizes free toxin and inhibits its further elaboration by preventing the growth of bacilli Damage to the heart and nerves of the critically ill patient can be reduced by prompt intravenous administration

of at least half of the initial therapeutic dose Intravenous antitoxin is especially indicated when the larynx is involved In mild or early cases the intramuscular injection is usually ample The lateral gluteal area is the site of choice As a rule at least 100 units per kilogram of body weight (50 units per pound) but never less than 5000 or 10 000 units should be administered In malignant or advanced cases crystalline penicillin G (300 000 units) may be given intramuscularly at the time of the antitoxin dose and should be repeated once or twice daily until marked improvement has occurred Penicillin may be given also by mouth (50 000 units buffered tablets) every 3 hours until repeated throat and nasal cultures are negative If the membrane fails to decrease within 48 to 72 hours the initial dose of antitoxin should be repeated and preferably another brand used To prevent the occurrence of untoward symptoms such as the Arthus phenomenon antitoxin of any kind should not be reinjected after an interval of 2 weeks

Desensitization Before antitoxin is administered 0 05 cc of a 1 20 dilution of antitoxin is injected intracutaneously in the left forearm If no local or systemic reaction occurs within 15 minutes 0 05 cc of a 1 10 dilution is injected subcutaneously if no reaction occurs 0 1 cc of undiluted antitoxin is injected subcutaneously then 0 5 cc is injected intramuscularly if no reaction results 0 1 cc is injected intravenously and if no reaction occurs the full therapeutic dose is administered Should a systemic reaction occur at any time 0 5 cc of adrenalin chloride solution (1 1000) should be administered without delay When sensitivity to horse serum is known to exist or is suspected as in allergic individuals bovine diphtheria antitoxin is recommended but the above outlined desensitization technic should be carried out with it In serum sensitive patients who are allergic also to bovine antitoxin repeated large intramuscular doses of penicillin are invaluable and curative If the first dose of penicillin elicits allergic symptoms its use should be curtailed or omitted

General Care Diphtheria patients should be kept flat in bed for at least a week and then activity in bed may be gradually permitted Toxic and dehydrated patients should be given a daily intravenous drip of 10 per cent dextrose solution alternating with isotonic amino acid solution The quantities are governed by the age of the patient degree of dehydration and height of fever Excessive amounts of intravenous fluid should be avoided Proctoclysis may be repeated several times daily if retained For the older child and adult the bedpan and urinal are imperative If the bowels are sluggish a daily tepid enema (1 tablespoonful of sodium bicarbonate to 1000 cc of water) is [illegible] water)

Drugs When the pulse is of poor quality caffeine (10 mg per kilogram of body weight) may be alternated with adrenalin chloride solution (0 3 cc 1 1000) giving at least two doses of each in 24 hours If the blood pressure is low a dose of pitressin (½ ampule) should be administered subcutaneously twice daily When the cervical glands are enlarged and tender an ice collar may give some relief Sulfonamides are of value only when a secondary infection is due to a sulfa sensitive pathogen

Diet At first only fluids should be given by mouth using the drinking tube dropper or spoon Water fruit juices diluted milk

provement is well under way A 100 mg ascorbic acid tablet should be included in the daily ration later on vitamins and iron should be added and continued for months

Complications *Laryngeal Diphtheria* The laryngeal diphtheria patient should be given 20 000 to 30 000 units of antitoxin intravenously as soon as possible and should be kept quietly in bed Needless excitement and exertion should be avoided Hospital care is most important at the time when the pseudomembrane sloughs off because respirations are likely to become more labored, and close medical supervision and constant intelligent nursing care are often necessary to save the life The electric suction apparatus has become an invaluable aid for the removal of mucus and debris from the pharynx larynx and trachea Repeated use

of carefully directed suction with the metal catheter has made recourse to intubation and tracheotomy less frequent Furthermore cautiously applied *suction causes less local* injury—as trauma and edema Moist air (croup tent) and the oxygen tent mask or *nasal catheter usually* facilitate breathing decrease cyanosis anoxia and toxicity However if cyanosis and retraction above and below the sternum increase and repeated and prolonged aspiration with the electric suction apparatus is ineffective intubation should be resorted to without too much delay If the tube is coughed up prematurely as it so often is when too small a tube is used or when the false membrane loosens immediate replacement of the tube (perhaps *the next larger size) may be necessary to* prevent fatal suffocation As a rule 2 or 3 days are long enough for the tube to remain in place longer than 4 days may cause pressure necrosis which produces scar tissue In severe cases especially in infants and young children nasal gavage feedings are advised for at least 4 or 5 days The moistened 8 F or 9 F catheter should be inserted only part of the way to the stomach to prevent coughing up of the intubation tube When relief fails to follow intubation tracheotomy may be necessary The lower tracheotomy operation is preferred Here again the tube should be removed as soon as breathing without it is possible Before its removal a stopper should be placed into the *lumen of the tracheotomy tube for increasing* periods of time to determine whether the patient has recovered sufficiently to breathe without the tube without again becoming cyanotic

Diphtheria Carriers Cultures from the nose and throat are usually negative within 2 or 3 weeks after the administration of an adequate initial dose of antitoxin Spraying of the nose and throat with a fresh solution of penicillin (10 000 units per cubic centimeter) six times daily usually speeds up recovery and negative cultures If the patient is allergic to penicillin manifested by edema of the tongue or the prompt appearance of a rash after the first dose of the antibiotic the drug should be discontinued

Virulence Test When diphtheria bacilli persist in the cultures without the presence of clinical symptoms a daily intramuscular dose of *crystalline penicillin G* (800 00 units) should be administered for sever days If the subsequent cultures remain po tive the Schick test and a guinea pig viru lence test should be performed If the form is negative and the latter proves the bacill to be nonpathogenic neither treatment n isolation is necessary The persistent pre ence of virulent bacilli in spite of liber doses of penicillin may warrant several thera peutic doses of roentgen rays or a tons lectomy

Louis W Sauer

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PERTUSSIS

(Whooping Cough)

Prevention Because pertussis is mor prevalent and causes more deaths during th first two years of life than do the three othe preventable contagious diseases smallpo diphtheria and scarlet fever combined im munization has been attempted as early i life as adequate immunity can be develope Three doses of fluid pertussis vaccine (tota dose 80 000 000 000 bacilli) conferred ade *quate and prolonged protection* to nearly a children when administered after the sixt month of life When the same dose was in *jected during the earlier months of* life a appreciable percentage of them failed t develop immunity Subsequently Sako Treuting Witt and Nichamin *showed* tha pertussis deaths could be prevented by thre monthly doses of alum precipitated pertuss vaccine injected during the first months o life More recently it was found that thre monthly doses of a slow absorbing antige (such as alum precipitated or aluminum hy droxide adsorbed) pertussin vaccine com bined with diphtheria and tetanus toxoi usually conferred good protection agains all three of these diseases when begun afte the sixth month of life A higher percentag of infants developed immunity than wher fluid antigen—plain mixed or *multiple*—wa

used Immunity tests performed 3 months or more after the final dose showed that 100 per cent had negative Schick tests 96 per cent had tetanus antitoxin levels of 0 1 unit or more per cubic centimeter of serum 83 per cent had positive pertussis agglutinogen skin tests (diameter of induration greater than 10 mm implies immunity) 24 hours later and pertussis complement fixation reactions were 3 or 4 plus in 83 per cent Furthermore it was found that when primary immunization was attempted before the sixth month of life four monthly doses of alum precipitated triple antigen yielded better protection than did three

Tests for Pertussis Immunity When primary immunization is attempted during the early months of life four monthly doses should be administered and a follow up immunity test (agglutinogen skin test agglutination complement fixation test) should be performed to determine whether adequate immunity has been conferred The skin test is simple to perform reliable and bleeding is unnecessary One tenth cubic centimeter of diluted agglutinogen is injected intracutaneously in the customary site on the left forearm An area of induration greater than 10 mm in diameter 24 hours later is evidence of immunity to pertussis

Administration of Slow Absorbing Antigens Alternate lateral gluteal regions (starting with the left proximal) are the preferred sites for alum precipitated antigen injections Syringes (1 cc) and needles (25 gauge ½ in) are rinsed only in distilled water and dried before they are sterilized preferably by dry heat (oven at 150° C for one hour) Each deeply administered dose is terminated with 0 1 cc of air The needle remains in place for a few seconds before it is quickly withdrawn It should not deviate from its original course (The infant is held firmly to prevent squirming) Immediately the site is gently massaged with sterile gauze Subsequent doses should not be administered near the site of a previous injection A deep circumscribed nodule may be palpated for a month or longer but the fluctuating or discharging cyst has been almost completely eliminated

Reactions Mothers should be forewarned that local and systemic reactions may occur If fever follows a meal should be reduced or omitted tepid water should be offered repeatedly during the next 12 to 24 hours and several small doses of aspirin should be given in a teaspoon of sugar water During hot weather excessive clothing covers and exposure to the sun should be avoided Regardless of concentration dosage type of antigen time interval between doses or age of infant no adverse systemic reaction other than transient fever is known to have occurred in any infant or child injected by the writer in over 20 years The only local reactions of importance followed alum precipitated antigen A subcutaneous nodule or an occasional alum cyst (miscalled sterile alum abscess) occurred Local reactions have been reduced in frequency and almost completely eliminated by the improved injection technic (*see* Administration of Slow Absorbing [illegible]

[illegible]

immunized and after intimate exposure is [illegible]

[illegible]

factors require further study

Failure to Confer Immunity Before one can conclude that pertussis vaccine has failed to confer immunity it is of importance to exclude *B parapertussis* infection The differential diagnosis can be made from nasopharyngeal cultures taken early in the disease or later by specific immunologic tests on the serum Failure to confer immunity may be due to one of the following causes

(1) Impotent antigen may result from
  (a) use of strains that lacked antigenicity
  (b) inadequate refrigeration — room temperatures above 10° C (50° F) are deleterious to cultures and vaccine
  (c) exposure in transit to prolonged high temperature
  (d) use of outdated vaccine
  (e) deleterious action of preservative
(2) Inadequate total dosage For sustained immunity infants less than 6 months of age require four monthly or bimonthly doses of alum precipi

tated antigen also booster doses at 2 and 5 years (*see section on Diphtheria Immunization Schedule*)

(3) Improperly spaced doses
  (a) too close together (monthly interval is best)
  (b) too far apart (more than 2 months)
(4) Inadequate antibody response
  (a) *exposure to pertussis before an* adequate antibody level has been attained
  (b) infants — premature immature frail or with intercurrent febrile diseases

Passive Immunization An intimately exposed nonimmunized child under 2 years of age should be injected promptly with the equivalent of 20 cc of pertussis immune serum–human or 2 5 cc human hyperimmune globulin If exposure occurred in the household the nonimmune infant to whom serum has been administered should be isolated from the patient or with the consent of the local health authorities taken from the premises until the pertussis patient is no longer contagious or until the exposed infant [illegible]

[illegible] develop the disease

The prophylactic effect of pertussis immune serum–human (20 cc) or human hyperimmune globulin (2 5 cc) administered promptly after exposure and the accelerated decline in pertussis morbidity and mortality in recent years have made prenatal *immunization* of expectant mothers by obstetricians an unnecessary procedure

Treatment Infants and frail young chil[illegible]

[illegible] hyperimmune globulin (2 5 cc) To desperately ill infants McGuinness Armstrong and Felton recommend that a dose be injected on each of 3 successive days to other young patients a dose every other day until three *doses* have been given Patients who fail to show improvement require additional doses Many infants under one year of age show improvement *within* a week Patients over one year of age may require larger doses especially if improvement fails to occur A dramatic reduction in the fatality rate has taken place Critically ill infants should be given intravenously a dose of 60 to 100 cc of the serum Reactions rarely follow After intramuscular injection local *discomfort* may continue for a day or two A slight transient fever occasionally occurs in less *than 1 per cent Patients* with a history of allergy may be skin tested with 0 1 cc of serum diluted with its full water content and again diluted 1 10 with sterile distilled water Skin testing with serum not so diluted may give a positive reaction A number of clinicians have reported human serum and globulin more effective than refined rabbit serum *and far less likely to cause allergic* reactions

General Care Most pertussis patients more than a few years *old* make uneventful recoveries Fresh dust free air and sunshine are beneficial A week or more in bed decreases the frequency and severity of the attacks of coughing and vomiting

The food should be easily digestible and rich in vitamins Excess of fluids iced drinks and chilled foods should be avoided as *paroxysms are thus precipitated* For young children puréed food such as vegetables strained meats soft boiled eggs mashed potatoes puddings junket cereals *and bread* soaked in warm milk are nutritious and usually well tolerated Cereals such as rice farina or cornstarch may be cooked first in half milk and half water later in undiluted milk In the case of young infants suction with a soft rubber bulb syringe may be applied before meals to rid the pharynx of mucus When vomiting is persistent five or six small feedings should be tried Gavage is not used since it provokes coughing and *vomiting When vomiting persists* oral medication should be decreased or entirely omitted for a day or so When fever and vomiting continue *retention enemas* four times daily of tepid water or 5 per cent dextrose solution are of value and may be administered by means of a *14 F* lubricated catheter attached to a 2 oz rectal bulb syringe The tip of the catheter is inserted for a distance of about 3 inches before *the* tepid contents of the raised bulb are slowly injected the catheter is pinched off before it

is withdrawn and the knees are kept together for an hour or more to prevent expulsion

Pertussis patients are reluctantly admitted to hospitals during the contagious stage [illegible] recovery In hospitals hypodermoclysis of normal saline or 5 per cent dextrose solution may be administered repeatedly Also repeated doses of serum can be given intravenously Isotonic amino acid solution should be used with caution and administered only when indicated Amigen by mouth is safer Infants with severe pertussis require expert nursing care Bactericidal lamps protect against air borne cross infection decrease respiratory complications and destroy exhaled pertussis bacilli Infants and frail young children not infrequently contract enteritis and may have convulsions Convulsions frequently cease soon after the infant has been placed in an oxygen tent The concentration should be maintained at about 50 per cent the temperature should never go below 20° C and the humidity should be kept above 40 per cent

DRUGS The age and weight of the patient the severity of the infection and complications determine the kind of drugs and dosage It is hazardous to try to check a severe cough completely by sedation This is especially true in the infant the frail child and any patient who already has a respiratory complication Profuse secretions should be coughed up and out of the bronchi at least several times each day Opium codeine and other sedatives such as the barbiturates should be used with caution preferably only at night to induce rest and sleep and to decrease vomiting The following prescription has been found of benefit

[illegible]

[illegible] to 1 teaspoonful or more once or twice at night for severe cough

When the paroxysms are severe and vomiting recurrent sleep and relief are often induced by a retention enema of sulfuric ether (25 per cent) in olive oil (75 per cent) given with a 14 F catheter and small bulb syringe every 8 hours for a week or longer The usual dose is 2 teaspoonfuls of the mixture for each year of age It is inflammable There is no danger of necrosis

CHEMOTHERAPY Sulfadiazine is the sulfonamide of choice because it is the most effective and least toxic Although of little value in the treatment of pertussis itself its use may be indicated when secondary infections due to sulfonamide sensitive pathogens occur

ANTIBIOTICS *Penicillin* is more effective in pertussis and less toxic than are the sulfonamides It is most useful in sulfadiazine resistant or sulfadiazine allergic patients with bronchopneumonia when the pulmonary complication is caused by a pneumococcus streptococcus or staphylococcus If desired both drugs may be given in alternate doses Penicillin may be given by mouth but the intramuscular route is preferred A dose of crystalline penicillin (300 000 units) may be used once or twice in 24 hours To minimize local trauma injections are rotated between the large muscles such as gluteal deltoid and thigh Treatment should be continued for 5 days or more A concentration of 5 mg per cent of free drug in the blood serum is usually adequate

Penicillin is quite effective in respiratory complications if given by mouth in adequate dosage Crystalline penicillin G has the advantage of stability without refrigeration A buffered tablet contains 50 000 or 100 000 units The drug should be given only on an empty stomach at 3 or 4 hour intervals Fasting should be maintained for at least 2 hours after each dose Not infrequently a transient diarrhea subsides within a few days after the drug is stopped When it occurs a boiled milk and a fruit and vegetable free diet should be followed

Streptomycin Streptomycin has been used to advantage when other measures have failed to produce desired results An increasing number of pertussis patients with pneumonia have responded rapidly The preferred method is an intramuscular dose every 12 hours It is important to rotate the site of injection The dosage recommended by the manufacturer should be closely followed Only in exceptional cases should streptomycin be used longer than 3 days In resistant pulmonary complications streptomycin

should be administered by nebulization and inhalation in a concentration of 50 mg per 1 cc of sterile isotonic sodium chloride solution, using about 1 cc every 3 hours Oral administration is of no value The most significant untoward effect has been injury to the eighth cranial nerve It is safer not to exceed 1 gm daily for a maximum of 4 or 5 days Recently, dihydrostreptomycin has been used without producing most of the untoward reactions from streptomycin

Chloromycetin Payne et al have recently reported on 50 cases of pertussis in children under 5 years of age, treated with chloromycetin This agent was extremely successful in curing the disease The dosage of the drug varied with the age of the patient, but most patients in Payne's group received 0 25 gm as the initial dose followed by 0 125 gm every 6 to 8 hours Aureomycin is not of value in pertussis

Complications Periodic examination of the young patient is advised so that complications can be detected early and treated as they arise Although most patients can be taken care of in the home those with complications and infants in congested homes or under circumstances where secondary infec

complications involve the respiratory tract, the gastro intestinal tract, and the central nervous system

In complications of the respiratory tract, such as bronchopneumonia, especially in infants and frail young children the oxygen tent or nasal catheter is beneficial, particularly when cyanosis or anoxia occurs If improvement does not follow repeated doses of human pertussis hyperimmune serum and chemotherapy and a specific type of pneumococcus is isolated from the expectoration or nasopharyngeal swab administration of the type specific antipneumococcic rabbit serum might accelerate recovery

Effective treatment when convulsions occur in the home is a hypodermic injection or two of sodium luminal or phenobarbital sodium (⅓ to 1 ampule, according to age) If convulsions continue, spinal drainage and continuous use of oxygen for several days are also of benefit

Gastro intestinal complications, such as enteritis, require careful selection of the proper food In young infants, during the acute stage, especially if the stools contain

due to a bacterial infection, sulfasuxidine in divided doses may be tried for several days to a week Additions to the diet should be made with caution After improvement is

and fats are most likely to intensify gastro intestinal upsets, especially diarrhea The patient's food tolerance should not be overstepped Ascorbic acid (25 or 50 mg daily) should replace fruit juices until recovery is complete

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TYPHOID FEVER

Typhoid fever is an acute infection caused by *Salmonella typhosa* and characterized by a rather typical clinical picture Management of this infectious disease has improved gradually over the past decade Prophylactic measures are being used more widely Recent advances in antibacterial therapy appear to offer better methods of treatment of the active infection

A detailed description of epidemiologic methods of control of typhoid fever is beyond the scope of this discussion These methods of control have been described by Anderson and Arnstein and include the proper disposal of sewage, the purification of water, and the prevention of food handling by carriers

Prophylactic Measures There are certain important prophylactic measures which deal with the care of the individual patient and the protection of susceptible individuals who may come in contact with the patient or with contaminated materials Infection with *Salmonella typhosa* almost always is due to the ingestion of contaminated food or liquid The infection is not air borne and therefore good technic should prevent the transmis [illegible] by *Salmonella typhosa* only if the organism reaches his mouth and gastro intestinal tract

Measures directed toward preventing the transmission of typhoid fever involve the following procedures

(1) The patient should be isolated and isolation precautions should be maintained if possible until negative results have been obtained on three stool cultures The windows of the patient's room should be equipped with adequate screens

(2) The urine and the feces should be disinfected This can be accomplished by mixing the urine or feces with equal amounts of a 1 1000 solution of bichloride of mercury or a 10 per cent solution of formalin and allowing it to stand an hour or more before discarding it The fecal material should be broken up before disinfecting Vomitus and other possibly infected excreta should be rendered harmless in the same manner

(3) The bedpan or urinal should be sterilized with steam, boiling water or bichloride of mercury solution Clothing bedding and utensils should be sterilized by heat or chemicals

(4) Attendants should scrub their hands with *soap and water and immerse them in a* 1 1000 solution of mercury bichloride or a 1 per cent solution of cresol after each contact with patients or soiled articles

(5) All cases of typhoid fever should be reported promptly to the public health authorities so that every effort can be made to determine the source of the infection

Persons exposed to infection should adhere to the following rules

(1) Susceptible individuals should avoid contact with the patient or with infected materials as much as possible

(2) Gowns and rubber gloves give some protection when the individual comes in direct contact with the patient

(3) The hands should be scrubbed frequently

(4) Any food or beverage which might be contaminated should be sterilized

(5) Typhoid vaccine should be administered to all contacts

Vaccination is a useful adjunct in the prevention of typhoid fever The protection obtained is only partial but the antibodies induced by the injection of killed typhoid bacilli usually are sufficient to provide a certain degree of immunity Vaccines usually contain 1 000 000 000 *Salmonella typhosa* organisms and 500 000 000 *Salmonella paratyphi*, *A* and *B*, organisms per cubic centimeter of suspension For an initial vaccination three injections should be administered The standard method has been to give the injection subcutaneously and the initial dose has been 0 5 cc of the vaccine Two subsequent injections of 1 cc each are given subcutaneously at intervals of 7 to 10 days The intracutaneous method of vaccination may be used if desired The effectiveness of intracutaneous vaccination in protecting the individual seems to be just as great as when the vaccine is injected subcutaneously, and reactions to intracutaneous vaccination are less frequent and less severe If the intracutaneous method is used the initial dose of vaccine is 0 1 cc the second injection is 0 15 cc, and the third injection is 0 2 cc The second and third injections should be given at intervals of 7 days If an individual is exposed frequently to typhoid fever, he should be revaccinated at least once every 18 months If he is revaccinated within this period of time a single intracutaneous injection *of 0 1 cc of typhoid vaccine is prefer*able, although a subcutaneous injection of 0 5 cc may be employed

Local reactions consisting of erythema, swelling tenderness, and aching often occur at the site of injection, particularly after subcutaneous injections Systemic reactions consisting of malaise, fever and aching occasionally occur

Acute Typhoid Fever ANTIBACTERIAL THERAPY Considerable optimism regarding the effectiveness of chloramphenicol (chloromycetin) in the treatment of acute typhoid

fever seems justified at this time The initial report by Woodward and co workers was encouraging Further studies have tended to confirm the original observations The optimal dosage of chloramphenicol still has not been established definitely Our present program of treatment is to give 50 mg of the drug per kilogram of body weight orally as an initial dose This initial dose usually is administered in divided amounts at hourly intervals over a period of 2 or 3 hours Subsequently a dose of 50 to 100 mg of chloramphenicol per kilogram of body weight is administered by mouth daily in divided doses For an adult the average dose is 3 to 4 gm as an initial dose and 0 5 gm every 3 or 4 hours thereafter The administration of the drug should be continued until the temperature has remained normal for 7 to 10 days Nausea and vomiting occasionally occur and may necessitate reducing the dose Other toxic reactions have not been noted The response to treatment with chloramphenicol usually is satisfactory The general condition of the patient improves the fever gradually subsides and the results of cultures of the blood become negative In some patients the gastro intestinal tract may continue to harbor *Salmonella typhosa* as evidenced by persistently positive results on culture of the stool but no symptoms are caused by this

In order to avoid the possibility of relapse McDermott has treated his patients with a prolonged course of therapy He gives the patient 6 gm of chloramphenicol daily during the first 3 days or until complete defervescence has occurred followed by approximately 1 5 gm daily for a total period of 28 to 30 days This may prove to be a preferable method of therapy if relapses are entirely eliminated

Treatment of acute typhoid fever with aureomycin streptomycin penicillin and the sulfonamide drugs has been disappointing However it is quite possible that in the future a combination of chloramphenicol and one or more of these other antibacterial agents may be the therapy of choice

If one is located in a community where bacteriophage can be made available use of this agent can be considered for the patient who does not respond to other forms of therapy In most instances however, the administration of bacteriophage is not practical and the clinical results have been inconclusive

General Measures The patient should be hospitalized if possible so that adequate facilities for treatment and for the handling of complications may be readily available Precautions to prevent spread of the infection as outlined under Prophylactic Measures should be instituted The patient must rest in bed Sleep and rest should not be disturbed except when absolutely necessary The use of sedatives may be indicated in order to insure rest especially if the patient is delirious Proper nursing care is important The bedclothes should be kept clean and dry The patient should receive a daily sponge bath with soap and warm water The teeth and mouth should be kept clean Oil or cream should be applied to the lips to prevent cracking

It is desirable for the patient to have a bowel movement at least once every other day Inasmuch as many of these patients are constipated the use of small enemas with plain water may be indicated Mineral oil given by mouth may be helpful Cathartics are contraindicated

Diarrhea occurs in only a small percentage of patients but at times may be a serious problem The diarrhea often can be controlled by altering the diet so that it contains only bland foods Bismuth subcarbonate in a dose of 15 grains (1 gm) every 2 or 3 hours may be helpful Opium derivatives should be avoided if possible However camphorated tincture of opium (paregoric) in doses of 4 cc (1 dram) can be used if other methods fail The use of this drug is not without risk for it may delay recognition of a perforation

At least a slight amount of abdominal distention occurs in most patients However an attempt should be made to prevent the development of any significant amount for distention can increase the strain on the respiratory and circulatory systems Distention usually can be avoided by providing a proper diet and using measures to prevent constipation such as enemas or mineral oil by mouth When distention is present hot stupes may be applied to the abdomen An enema a rectal tube or gastric suction may be of value

DIET As in any infectious disease, an adequate diet is essential In the past the diet of a patient suffering from typhoid fever was rigidly restricted Most clinicians now feel that the patient should be allowed to eat a diet of his own choosing providing the foods selected are easily digestible, nonirritating and contain an adequate amount of calories, proteins vitamins and minerals The difficulty usually is in getting the patient to take nourishment Patience, tact, and regard for the patient's taste in food are often necessary, if he is to secure an adequate diet Small frequent feedings are preferable to large feedings If the patient is toxic or delirious a fluid diet may be all that can be administered Carbonated beverages (not iced), broth, fruit juices or cereal beverages may be tolerated The carbohydrate intake can be increased by adding lactose to lemonade

Supplemental intravenous administration of a solution containing 5 per cent glucose and physiologic saline solution or a solution containing 10 per cent glucose in distilled water usually is necessary in the seriously ill patient If the patient is not able to take an adequate diet over a prolonged period, or if marked anemia is present whole blood should be given by transfusion Small transfusions of 150 to 250 cc of blood every 3 or 4 days are more effective than single transfusions of 500 cc

As soon as possible soft bland foods should be added to the diet The following foods may be tried white bread or toast, well cooked and strained cereals puddings without fruit or nuts, butter and cream, tender meat, fish, or fowl, potatoes, macaroni, and refined rice jelly, sugar, and plain candy Other foods may be added as soon as the patient can tolerate them although foods known to be irritating to the bowel should be avoided If diarrhea or distention is present, it may be necessary to reduce the amount of carbohydrates ingested

Management of the Convalescent Period The patient should be managed carefully during this period, for relapses occur in a significant percentage of cases Rest in bed should be continued for at least a week after the patient has become afebrile Changes in the diet should be made cautiously and the effect of these changes should be observed carefully

Treatment of Complications CIRCULATORY COLLAPSE This complication is probably the most important cause of death in typhoid fever Myocarditis and capillary dilatation often occur during the course of typhoid fever When these conditions become marked shock ensues Unfortunately, we have no satisfactory treatment for the shock which occurs in infectious diseases The cautious intravenous administration of whole blood or fluids may be helpful Oxygen should be administered, preferably by a Boothby Lovelace Bulbulian mask, although an oxygen tent can be used in certain instances Digitalis is of no avail unless there is actual cardiac decompensation The patient should be kept warm and inactive

INTESTINAL HEMORRHAGE The patient with typhoid fever always should be watched carefully for the development of this complication If bloody stools are noted, or if there is a sudden drop in temperature accompanied by a rising pulse rate, food should be withheld Sodium phenobarbital in a dose of 2 grains (0 13 gm) given hypodermically every 4 to 6 hours may produce sufficient sedation In certain instances morphine sulfate will be required, but it should be used cautiously In order to avoid the exertion of getting onto a bedpan stools should be passed on an absorbent pad If the blood pressure falls, or if the bleeding has been profuse, transfusions of whole blood are indicated The blood should be administered slowly in order to diminish any danger of dislodging the clot The intravenous administration of some suitable preparation of vitamin K may be helpful It is always difficult to know when bleeding has ceased However, if the blood pressure and pulse remain relatively normal for 24 hours, and if there is a cessation of frequent bloody stools it is usually safe to assume that significant bleeding has ceased Then small feedings of bland foods can be resumed

THROMBOPHLEBITIS The affected extremity should be elevated and warm packs applied If the prothrombin time is not elevated, the carefully controlled administration of dicumarol seems indicated in order to reduce the danger of a fatal pulmonary

embolus Anticoagulant therapy possibly may increase the risk of hemorrhage However, hemorrhage on this basis usually can be controlled Ligation of the femoral vein may be performed if such a procedure appears indicated However it is only rarely that such a procedure is advisable

OTHER COMPLICATIONS Intestinal perforation is a surgical problem and should be treated as an emergency Acute cholecystitis usually responds to symptomatic measures although surgical treatment may be necessary in certain instances Osteomyelitis usually will require surgical intervention

Treatment of Typhoid Carriers The problem of eradicating *Salmonella typhosa* from the stools and urine of patients who continue to harbor the organisms still has not been solved satisfactorily When the organisms are present in the bile cholecystectomy should be considered However this procedure does not eliminate the organisms from the bowel or from the bile in all cases Chloramphenicol in doses of 0 5 gm every 3 hours for 2 weeks can be tried but this drug may not be effective in eliminating *Salmonella typhosa* from the biliary or intestinal tract Sulfasuxidine sulfaguanidine and streptomycin have been reported as curing an occasional patient but in most instances these drugs are ineffective All typhoid carriers should be instructed in the methods of disinfecting excreta They should not be permitted to handle food Every carrier should be reported to the local department of public health

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SALMONELLOSIS

Bacteria classified as Salmonella are capable of producing varying types of clinical infection On the basis of clinical manifestations these infections due to Salmonella may be divided into three main types (1) Salmonella fever (enteric fever paratyphoid fever) (2) Salmonella enteritis and (3) a septicemic type with localization of infection almost anywhere in the body From a bacteriologic standpoint every Salmonella strain is potentially capable of producing any of these clinical types However, there is a tendency for certain specific strains to produce certain specific clinical manifestations Treatment of necessity must include antibacterial therapy directed toward the particular strain of Salmonella and supplementary measures directed toward the particular [illegible]

by

as

typhoid fever has a rather specific clinical course and therefore has been discussed separately from the other forms of salmonellosis

Anderson and Arnstein describe epidemiologic methods of control of Salmonella infections and the proper disposal of sewage purification of water supplies and the prevention of food handling by carriers Most Salmonella infections can be transmitted by animals as well as by man Therefore control measures include the inspection of animals slaughtered for meat and the supervision of other foods obtained from animal sources

The prophylactic measures which deal with the care of the individual patient and the susceptible individuals who are in contact with him are the same as those employed against typhoid fever A certain amount of protection against infections caused by *Salmonella paratyphi A* and *paratyphi B* usually can be obtained by vaccination with the usual typhoid paratyphoid vaccines The method of vaccination is the same as that outlined for typhoid fever

Treatment of Salmonella Fever (Paratyphoid Fever Enteric Fever) Although

nantly when positive cultures of the blood or stool are obtained

ANTIBACTERIAL THERAPY Judging from the results obtained in the treatment of typhoid fever it appears that chloramphenicol (chloromycetin) probably will also be effective in the treatment of some other forms of Salmonella fever Of course, further extensive

investigations will be necessary before a final evaluation of this type of therapy can be made. An initial oral dose of 50 mg of chloramphenicol per kilogram of body weight appears indicated This initial dose usually should be administered in divided amounts at hourly intervals over a period of 2 or 3 hours Subsequently a *total of 50 to 100 mg* of chloramphenicol per kilogram of body weight is administered by mouth daily in divided doses For an adult the average dose is 3 to 4 gm as an initial dose and 0 5 gm every 3 or 4 hours thereafter Nausea and vomiting occasionally occur with this dosage and may necessitate reducing the dose Other toxic reactions have not been noted

No evidence has been presented yet to indicate that aureomycin will be of much value in Salmonella fever Symptoms at times appear to be relieved when this drug is administered but cultures remain positive The use of streptomycin in the treatment of Salmonella fever also has been disappointing Again a symptomatic response sometimes is obtained but cultures remain positive The sulfonamides appear to be of little if any value

General Measures and Diet The general measures and diet outlined under Treatment of Typhoid Fever are equally applicable to other forms of Salmonella fever

Treatment of Salmonella Enteritis Any strain of Salmonella can cause enteritis but *Salmonella typhimurium* and *Salmonella enteritidis* are the predominant organisms found in this type of infection

Antibacterial Therapy Preliminary studies by Collins Paine Wells and Finland suggest that aureomycin may be of value in certain cases of Salmonella enteritis Aureomycin should be administered to adults in doses of 500 to 750 mg every 6 hours Aureomycin is quite irritating to the gastro-intestinal tract and may tend to increase the nausea and diarrhea No reports as to the effectiveness of chloramphenicol (chloromycetin) in Salmonella enteritis have [illegible]

most varieties of Salmonella do not respond to sulfonamides Streptomycin has not been found of much value

General Measures. General measures, including isolation and rest in bed are necessary in most cases. In the seriously ill patient careful nursing care is important Bismuth subcarbonate in a dose of 15 grains (1 gm.) every 2 or 3 hours may be helpful in controlling the diarrhea Camphorated tincture of opium (paregoric) in a dose of 4 cc (1 dram) can be used much more safely than in typhoid fever If the patient is very toxic oxygen in high concentration should be administered by a face mask

Diet A bland diet with low residue should be prescribed If the patient is very toxic a fluid diet may be all that can be administered Carbonated beverages (not iced) broth or cereal beverages may be tolerated The supplemental intravenous administration of 5 per cent solution of glucose and physiologic saline solution often is necessary in order to maintain the fluid balance If the patient is very toxic or if marked anemia is present whole blood should be given by transfusion As soon as the patient is in a condition to take soft foods the following may be tried white bread or toast well cooked and strained cereals puddings without fruit or nuts butter and cream tender meat fish or fowl potatoes macaroni refined rice jelly sugar plain candy Other foods may be added cautiously as soon as the patient can tolerate them

Treatment of Localized Salmonella Infections This type of infection usually is a complication of Salmonella bacteremia *Salmonella choleraesuis* is the organism most apt to produce these localized lesions

Antibacterial Therapy No chemothera

may be effective no conclusive studies have been reported as yet

Surgical Measures Some of these localized infections due to Salmonella are amenable to surgical drainage or excision The administration of streptomycin by intramuscular injection or chloramphenicol by mouth immediately before and for a few days after surgical treatment may help to prevent further dissemination of the infection

Treatment of Salmonella Carriers Inasmuch as Salmonella are frequently excreted in the feces during convalescence fro

infections due to this type of organism the persistence of organisms in the stool for several weeks after the acute infection need

should be instructed in methods of disinfecting excreta Public health authorities should be notified None of the antibacterial agents have been proved to be effective in eliminating the organism from the stool Chloramphenicol may be of value in some cases

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BACILLARY DYSENTERY

(Shigella Enteritis)

Bacillary dysentery is caused by a group of organisms classified as Shigella These organisms produce a variable type of clinical picture ranging from a mild diarrhea without fever to a severe systemic process accompanied by high fever almost constant diarrhea and circulatory collapse

Prophylactic Measures Felsen has shown that the control of bacillary dysentery depends upon the elimination of sources of infection the prevention of transmission of organisms and the protection of susceptible individuals In the United States general sanitary measures usually prevent the occurrence of large epidemics However small groups of cases do occur from time to time and during disaster or war epidemics may occur

Sources of infection are best controlled by isolating patients and treating known carriers Susceptible individuals are best protected by insuring the ingestion of only uncontaminated food and water The use of prophylactic chemotherapy in certain situations seems advisable

ISOLATION OF THE PATIENT The patient should be isolated until cultures of the stool give negative results The stools should be rendered harmless by mixing with equal amounts of a 1 1000 solution of bichloride of mercury or a 10 per cent solution of formalin Bedpans utensils clothing and bedding should be sterilized by heat or chemicals Attendants should scrub their hands carefully after coming in contact with patients or contaminated articles

MANAGEMENT OF PERSONS EXPOSED TO INFECTION Any food or water which might be contaminated should be sterilized or discarded The hands should be washed carefully after any contact with patients or infected materials Prophylaxis with sulfadiazine streptomycin or one of the newer antibiotics may be indicated in certain instances

Treatment of Acute Bacillary Dysentery GENERAL MEASURES In mild cases of bacillary dysentery the disease usually can

supportive measures are important adjuncts to the antibacterial therapy Strict rest in bed is of importance Sedatives may be necessary to insure proper rest Careful nursing care is indicated for the seriously ill patient

Fluids lost through diarrhea or vomiting must be replaced by appropriate methods in order to avoid the effects of dehydration Liquids can be taken orally unless the patient is nauseated and vomiting If the oral intake is inadequate the intravenous administration of physiologic saline solution or of 5 per cent solution of glucose is indicated Transfusions of whole blood are of value in the treatment of seriously ill patients especially if there is any hypoproteinemia or anemia

Control of the diarrhea and relief of pain can be obtained by administering camphorated tincture of opium (paregoric) in doses of 4 cc (1 dram) or powdered opium in doses of 2 grains (0 13 gm) orally every 3 or 4 hours Bismuth subcarbonate in doses of 15 grains (1 gm) or milk of bismuth in doses of 4 cc (1 dram) may be added if the diarrhea is severe Hot stupes to the abdomen

may help alleviate the pain If tenesmus is [illegible] to liquids If there is much vomiting or distention, it may be advisable to withhold liquids and food for a short period and rely on parenteral administration of fluids to maintain the fluid balance As soon as possible a liquid diet should be resumed Broth carbonated beverages (not iced), and cereal beverages are usually well tolerated Sugar may be added in moderate quantities As soon as the diarrhea has been controlled a bland diet can gradually be started The following foods may be tried white bread or toast, well cooked and strained cereals puddings without fruit or nuts, butter and cream tender meat, fish or fowl potatoes macaroni, and refined rice, jelly, sugar and plain candy This bland diet should be continued for several days and then a normal diet can be resumed cautiously In the seriously ill patient vitamins of the B complex should be administered parenterally during the acute phase If the convalescence is prolonged, the diet should be supplemented by vitamins administered orally

ANTIBACTERIAL THERAPY In the mild forms of bacillary dysentery the use of chemotherapeutic agents usually is not necessary However, in all cases except the mild ones some form of chemotherapy is indicated

Sulfonamides Many of the sulfonamide drugs exert a bacteriostatic effect upon bacteria of the genus Shigella according to Hardy and Watt However, not infrequently sulfonamide resistant strains are encountered Sulfadiazine is an effective form of therapy in many severe forms of bacillary dysentery, especially when it is given within the first 24 hours of symptoms Diarrhea and abdominal pain usually cease within a day or two after the onset of treatment with this drug The temperature becomes normal in about the same period of time The inflammatory changes in the bowel cease to progress However, Smith has shown that actual healing of the mucosal lesions does not take place as rapidly as does the symptomatic relief If the inflammatory process has progressed to the stage of ulceration, healing may not be complete for several weeks Therefore, the administration of sulfadiazine early in the course of the disease is important if the inflammatory changes are to be readily controlled

Administration of sulfadiazine should be started as soon as a tentative diagnosis of bacillary dysentery has been made An initial dose of 60 grains (4 gm) of this drug is administered by mouth and a dose of 15 grains (1 gm) should be given subsequently every 4 hours If the patient is dehydrated, intravenous administration of fluids should be started soon after the initial dose of sulfadiazine so that there will be an adequate urinary output If the patient is not dehydrated, fluids by the oral route alone usually will suffice However, it is imperative that the patient receive enough fluids to insure a urinary output of about 1500 cc The administration of sodium bicarbonate in doses at least equal to the doses of sulfadiazine is advisable The administration of sulfadiazine should be continued for a minimum of 72 hours and for at least 48 hours after the temperature has returned to normal If the use of the sulfonamide is continued for several days, the cells in the urine and the number of leukocytes in the blood should be watched carefully

The poorly absorbable sulfonamides, such as succinylsulfathiazole (sulfasuxidine) or sulfaguanidine have been shown to be effective in many cases The results, in general are not as good as those obtained with sulfadiazine However, if a situation arises wherein the patient cannot be kept under close observation, the use of succinylsulfathiazole (sulfasuxidine) usually will be the therapy of choice Succinylsulfathiazole should be given in doses of 75 grains (5 gm) every 6 hours for a minimum of 5 days and preferably, until the results of rectal cultures are negative

Streptomycin If the patient does not respond well to sulfadiazine, a trial of streptomycin is indicated, for most strains of Shigella are sensitive to streptomycin Pulaski has obtained satisfactory results using a daily dose of 3 gm of streptomycin orally in divided doses

In certain instances both the oral and intramuscular administration of streptomycin seems indicated An intramuscular injection of 0 5 gm of streptomycin every 8 hours and

an oral dose of 0 5 gm every 8 hours is a satisfactory schedule for adults Dihydro streptomycin may be substituted for strep *tomycin if desired The intramuscular use of* streptomycin is contraindicated if there is *any renal insufficiency*, but oral therapy usually can be continued, inasmuch as there is little absorption of streptomycin from the gastro intestinal tract

Aureomycin From preliminary laboratory *studies* it would appear that aureomycin will be an effective agent in the treatment of bacillary dysentery Further clinical investi gation will be necessary before final con clusions can be reached regarding the place of aureomycin in the treatment of this in fection It is quite possible that aureomycin may become the drug of choice in the treat ment of bacillary dysentery

Chloramphenicol (*Chloromycetin*) In *vitro, the Shigella organisms are sensitive to* chloramphenicol Therefore use of this drug may prove to be an effective form of therapy No clinical trials have been reported as yet

Complications ARTHRITIS This complica [illegible]

gm) every 4 hours often will give symp tomatic relief

CHRONIC BACILLARY DYSENTERY This com plication is a form of ulcerative ileocolitis which occasionally follows an attack of severe bacillary dysentery Streptomycin adminis tered orally in a dose of 1 gm three times daily is often effective in eliminating the in fection Aureomycin in doses of 750 mg *every 6 hours may* be effective The sulfona mides, either sulfadiazine or sulfasuxidine, or both are of proved benefit if the organ isms are not sulfonamide resistant Chlo ramphenicol may prove to be of considerable value, however, clinical studies of the effec tiveness of this substance have not been re *ported as yet As in acute* bacillary dysentery, particular attention should be paid to the diet The foods previously mentioned under "Treatment of Acute Bacillary Dysentery" will serve as a basic diet, and additions to this diet can be made cautiously Supple mental use of vitamins may be indicated if *the disease has been of* long duration

OTHER COMPLICATIONS Localized infec tions, such as endocarditis and meningitis, are rare These complications should b treated with vigorous antibacterial therap At the present time sulfadiazine given orall *or streptomycin* given intramuscularly in th doses previously advised appear to be th drugs of choice In the future aureomyci or chloramphenicol *may prove to be a su* perior therapeutic agent for these seriou infections

DONALD R NICHOLS

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CHOLERA

Prevention Since cholera is essentially a disease dependent on poverty, overcrowding, and bad hygienic conditions it can best be prevented by improving the standard of liv ing which includes education public and personal hygiene, modern sewage disposal control of vermin, refrigeration and control of food and drink Cholera has disappeared from many communities as a result of these improvements alone but it may occur at any time anywhere when conditions favor it The outbreak in Egypt in 1947 is an example of such an occurrence

Because man, so far as is known is the only source of cholera, it could be extermi nated if all patients could be strictly isolated and all carriers quarantined Unfortunately, this cannot be accomplished

During epidemics or in endemic areas water for domestic use should be efficiently chlorinated boiled or obtained from sources known to be free from contamination Food should be handled carefully, refrigerated and protected from insects Flies and vermin must be controlled by screens traps, swat ters, repellents and insecticides Most effec tive are preparations of *DDT which can be* sprayed into closed spaces or painted on walls and screens of rooms latrines and garbage racks Feces from cholera patients or carriers should be disinfected before dis posal or buried in deep covered pits Feces

in open latrines should be sprayed or dusted with DDT

VACCINE The value of vaccination against cholera is uncertain Vaccination alone has never controlled an outbreak and vaccinated persons may acquire a false sense of security To be effective vaccine must contain antigens similar to those of the strain or strains rampant at the time Immunity evoked by vaccine does not last more than several weeks or months If used vaccination with heat killed vibrios consists of an initial dose of 0 5 cc followed in 7 to 10 days by 1 cc ses of there

mpor tant factor is to eat or drink food or beverages which are known to be safe or which have been thoroughly cooked or boiled Sterilized food and drink may be infected later by flies or by hands soiled with feces Food may be contaminated by soiled containers or by washing or mixing it with polluted water or ice Uncooked vegetables and fruits should not be eaten Uncontaminated water or water sterilized by boiling or by chemicals must be used Vigilant supervision of the operations of native Asiatic or African servants and cooks and of their health is necessary

Fatigue and excesses of any kind must be

tives increase susceptibility to cholera

Treatment Prompt and vigorous treatment is imperative and management must be regarded as an emergency measure Treatment begun within a few hours of the onset is most successful Proper treatment can be given easily to small groups of patients when adequate medical and nursing aid and adequate hospital facilities are available However in places where cholera occurs and for the reasons that it occurs conditions often are primitive Under such conditions a sudden outbreak with hundreds of patients at once makes the care of all but a few impossible and accounts for the high mortality rate Treatment includes the management of the patient and of the epidemic as well

Patients should be cared for in hospitals whenever possible where therapy and isolation are managed more easily During an epidemic or otherwise patients with mild attacks or those suspected of having cholera should be kept in bed isolated and observed Their excreta should be examined carefully for *V comma* sterilized or properly buried

Treatment should be commenced as soon as possible after a history is taken a physical examination is made a blood count and urinalysis are done the pressure and the specific gravity of blood are measured and smear and culture of the stool are made All data including temperature volume of the stool vomitus and urine and amounts of fluid ingested and injected should be recorded in chart form Even if no vibrios can be seen in smears of the stool treatment should be started since cultural studies and identification require several days for completion

FLUIDS Water containing 1 per cent sodium bicarbonate should be offered in small amounts every 15 minutes if there is no vomiting but more rapid rehydration and remineralization are urgent in severe attacks Intravenous injection of isotonic solution of sodium chloride warmed to near body temperature should be given at once at the rate of 60 to 100 cc a minute in amounts of 1000 to 2000 cc depending on the size of the patient and the specific gravity of the blood About 300 cc. of 2 per cent solution of sodium bicarbonate are added to the first infusion and to subsequent ones if collapse or acidosis is evident Febrile reactions often occur from solutions prepared under unfavorable conditions but the urgency of treatment outweighs the dangers therefrom If veins are inaccessible or cannot be entered the intramedullary route of injection into the sternum or tibia may be used

Amazing improvement often occurs rapidly but in many instances purging and vomiting continue collapses recur and require repeated injections sometimes every 3 or 4 hours Relatively enormous amounts of fluid are needed for cholera As much as 10 000 cc has been infused continuously within the first few hours and more than 14 000 cc in a 24 hour period Injections may have to be given over 2 or 3 days

The specific gravity of the blood must be

measured at the bedside, preferably with

than 1 058, more fluid is needed If actual measurements cannot be made, judgment as to the amounts needed must be guided by the clinical response, blood pressure, pulse rate, consistency of the blood, and output of urine Care must be taken not to give too much lest overfilling occur, signaled by rest lessness palpitation, substernal oppression cough, or edema

Sterile, pyrogen free isotonic solution of sodium chloride (9 gm sodium chloride to 1000 cc water) is the fluid of choice Some clinicians prefer to add 5 per cent dextrose, *but not more than 400 gm of glucose should* be given in 24 hours Thiamine chloride, 1 mg for every 25 gm of dextrose may be

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Routine Care The management of a cholera patient is otherwise the same as for any severe infection of the *gastro intestinal* tract Patients should be strictly isolated Clothing, bedding, and personal articles should be sterilized by washing with soap and hot water, by boiling, or with chemicals Alvine discharges and vomitus must be dis infected with 1 1000 solution of mercury bichloride or other germicide before dis posal in a sewage system Otherwise they should be emptied into a deep, covered pit, remote from any water supply or kitchen Attendants must be taught to observe rigid rules of hygiene Flies and vermin must be exterminated

The patient should have a minimum of disturbance During periods of chill and col lapse the body should be covered and warmed to normal temperature with hot water bottles or heated coverings Water and liquid or semisolid food may be given, if desired by the patient Restlessness may be treated with barbiturate compounds or with morphine The latter may be used for the severe pain of muscular cramps Complications are uncommon but should be anticipated and treated

Drugs Digitalis or other cardiac and cir culatory stimulants are not needed unless heart disease itself is present Medicaments, such as purgatives, enemas, intestinal anti septics, constipating agents, opium, specific immune serum, bacteriophage and others *are of no proved value and are not* recom mended

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Convalescence Recovery, even without treatment, is often surprisingly rapid but rest in bed should be enforced reasonably for several days Subsequent fatalities may occur suddenly, some of them perhaps from em bolism Fluid and soft, easily digested foods both preferably warm or hot, may be offered as soon as desired by the patient Patients should not be released from control until *their stool cultures no longer contain V comma*

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Treatment

4

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PLAGUE

Prophylaxis The control of plague like that of cholera is largely a problem of economics and education With the abolition of poverty and squalor and an improvement of the standard of living the conditions favoring the spread of plague from rodents to man and from man to man by way of the flea or otherwise disappear spontaneously However since poverty ignorance and overcrowding still persist in many areas of the world plague is an ever present menace which must be guarded against by other measures

Extermination of the Source and Vector Rats or other rodents which harbor plague bacilli and their vectors must be exterminated or prevented from coming in contact with people Concrete foundations or other ratproofing of buildings is desirable but expensive Ships coming from endemic areas should be fumigated with hydrocyanic acid gas or sulfadioxide and hawser shields provided when docked Rats may be trapped with snap traps but according to Macchiavello they are effectively controlled by a fluorine raticide called 1080 Technical difficulties often interfere with destruction of rodents and many believe that an attack on the flea vector with the insecticide DDT is of great importance Persons in endemic or epidemic areas should be dusted with DDT in powdered talc or wear clothing impregnated with it Repellent agents such as pyretherum are less reliable

Chemoprophylaxis Daily oral administration of 3 gm of sulfadiazine apparently was successful in preventing plague in small groups of exposed persons The method has not been tried in field tests and it is questionable if it is justified or reliable in uncontrolled groups because of the toxicity of the drug

Vaccine The value of antiplague vaccine is not agreed upon and its use tends to give a false sense of security Furthermore there are different serologic varieties of plague bacilli which require a high degree of specificity of the vaccine Living "attenuated" plague bacilli have been used as vaccine with reported successful results in Africa but the danger inherent in such a practice does not justify its general use The injection of antiplague serum to provide passive immunity is not warranted

Quarantine. Quarantine as managed by specially trained public health officers with recognized authority to enforce rules and co-operation on the part of the public is of great importance The dissemination of instruction and advice paves the way for effective control Patients and persons in contact with patients should be isolated

Physicians and attendants dealing with an epidemic should wear clothing impregnated with DDT or insect proof clothing boots and gloves Those in contact with pneumonic plague should wear a complete hood or thick mask over the nose and mouth to avoid inhaling bacilli suspended in the air

Treatment The general management is the same as for any severe infectious disease Bed rest is imperative Diet and fluid intake should be adequate Morphine may be needed for extreme restlessness or painful buboes Oxygen is helpful when pneumonia is present The circulatory system requires especial attention but digitalis is not necessary Buboes should be covered with hot moist compresses and not incised If tense with pus aspiration with a hollow needle is advised

At present according to numerous reports sulfadiazine is the drug of choice for specific therapy but well controlled large scale studies have not been made Early treatment is most effective The initial dose of sulfadiazine is 4 gm followed by 1 gm. every 4 hours In comatose or unco operative patients sodium sulfadiazine may be given intravenously

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[illegible] Treatment [illegible]

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TETANUS

That the treatment of tetanus is not particularly satisfactory is evident from the controversial nature of articles on the subject Nevertheless, recognition of the limitations in the management of patients with clinical manifestations of tetanus serves to clarify some of the controversial issues and properly places emphasis upon those measures which provide the minimum of danger to the patient At the same time, the unsatisfactory nature of treatment makes all the more important the widespread utilization of the recently demonstrated fact that tetanus is an entirely preventable disease

Since only those patients who have not already a lethal amount of toxin in the central nervous system can be saved practical treatment should be formulated (1) to control life endangering spasms or convulsions while maintaining adequate oxygenation and hydration of the patient and (2) to prevent additional tetanus toxin from reaching the nervous system At the same time, one should organize treatment so as to eliminate procedures which might prove fatal either because the procedure itself is inherently dangerous or because it may induce severe spasms

Control of *Spasms* and Maintenance of Hydration and Oxygenation Death from asphyxial spasms or exhaustion is prevented by sedation and by guarding the patient from all unnecessary stimuli The latter measure entails strict seclusion in a quiet darkened room with a minimum of handling of the

stantly balance the expected worth of each procedure against its possible disturbance to the patient

The objective in sedation is to afford relief from spasms and convulsions without undue depression of the respiratory and cardiovascular systems It is desirable to utilize agents which will maintain a fairly steady depth of sedation and a large degree of flexibility, because the pathway between life endangering spasm and serious depression of vital functions is frequently narrow Solution of tribromethanol (avertin) has proved quite satisfactory when used in small amo

frequently repeated Usually a fairly large initial dose is required followed by smaller maintenance doses According to the severity of the disease, the initial dose may be 30 to 90 mg per kilogram of body weight and the maintenance doses 10 to 30 mg per kilogram Sometimes difficulty is encountered because the solution is expelled from the rectum Usually this is due to inadequate relaxation, either because no sedation has been given previously or because the interval between doses has been too long The administration of sodium amytal intramuscularly or intravenously in amounts up to 5 mg per kilogram of body weight will usually produce sufficient relaxation so that a solution of *tribromethanol may be used* Considerable caution must be exercised in giving sedatives intravenously to patients with tetanus lest in one's haste to control a severe spasm an amount of the sedative be given which proves to be dangerously depressing once relaxation occurs The use of dilute solutions injected slowly will diminish this hazard In some cases of severe tetanus, sodium amytal may be needed to supplement the rectal medication, especially at times when severe spasms might be precipitated by necessary manipulations of the patient Capsules of seconal, 100 to 500 mg at a time, inserted into the rectum are a practical means of sedation in the milder cases or dur

reaction of the patient afford the best guide as to the maintenance dosage of sedatives required

Severe pain and great terror are engendered by the spasms of tetanus These can be relieved by sedation in mild and moderately severe cases Painful spasms cannot be safely eliminated at all times in severe cases In such instances small to moderate doses of an analgesic such as 0 6 gm of aspirin may greatly aid in the management of the patient Demerol hydrochloride, 100 mg, with less respiratory depressant action may be preferable to morphine, although the latter has been used successfully *in many cases.*

The parenteral administration of magnesium sulfate has numerous advocates, but with this drug the relief of spasms has not

te, whereas alarming depres-

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LEPROSY

Prevention Since observation has suggested intimate and prolonged contact with a leper to favor transmission of the disease to others, a most important factor in prevention is the isolation of lepers during the active stages of the infection Of 700 cases studied by Rogers, 80 per cent had lived in the same house with a patient, and 30 per cent had shared a bed with one Other studies showed that only 3 to 5 per cent of exposed persons were infected With reasonable care, however, the danger of transmission is small, especially to adults who observe hygienic measures The patient should be instructed how to avoid infecting others and, if co operative, is no serious menace except to infants It is best to remove infants from leprous households There appears to be a strong familial tendency or predilection to contract the disease when exposed to it Patients who have recovered from leprosy clinically and who have no discharging lesions are regarded as non-infectious and may live unrestricted lives except for reporting for periodic examinations for evidence of relapse The transmission of leprosy by way of tattooing was observed in 2 soldiers

Treatment Patients are best treated in a leprosarium, such as the one at Carville, La, where the disease is best understood and managed by experienced and interested personnel Efforts are directed to make life attractive and as free from restriction as is safe The general health should be improved by measures akin to those needed for tuberculosis Cleanliness, diversion, occupation, [illegible] are all [illegible] proving the morale of patients Frequent hot baths and a change of climate are often helpful

According to McCoy, although segregation has not been proved to be an effective public health measure, patients with "open" leprosy should be isolated Secretions and excretions should be destroyed by heat or otherwise

SPECIFIC TREATMENT Antibiotics and the commonly used sulfonamide compounds have no effect in leprosy except to control secondary pyogenic infections caused by bacteria sensitive to the effects of these agents However, three new compounds, namely, *promin*, *promizole*, and *diazone* are of value Since they have been in use, the number of patients discharged as arrested cases from the National Leprosarium at Carville in 1946 was double and the death rate one half that of any previous year The effects of promin and diazone are similar, but the latter has the advantage of being tolerated in oral dosage of 1 gm daily for long periods According to Faget and his co workers, promizol in doses gradually raised to 6 gm daily is well tolerated and clinical improvement occurs faster than after therapy with promin or diazone Improvements in patients with advanced lepromatous leprosy may appear after 6 months or more of treatment Further study is needed Toxic reactions such as fever, malaise, hematuria, anemia, and others occur

Chaulmoogra oil and its various derivatives are recommended by some observers but are considered as drugs of unproved value by the majority They have little or no curative value and their unpleasant side effects probably outweigh any advantage which may occur from their use

Roentgen ray or light treatments have at times a favorable influence Large doses of vitamin B_1 (thiamine chloride) 100 mg intravenously, twice daily, are said to relieve the pain of neuritis

Complications require appropriate medical, orthopedic, or surgical care

HOBART A REIMANN

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Control of Spasms and Maintenance of Hydration and Oxygenation Death from asphyxial spasms or exhaustion is prevented by sedation and by guarding the patient from all unnecessary stimuli The latter measure entails strict seclusion in a quiet darkened room with a minimum of handling of the patient even for examinations bathing feeding obtaining laboratory specimens and the administration of drugs One must constantly balance the expected worth of each procedure against its possible disturbance to the patient

The objective in sedation is to afford relief from spasms and convulsions without undue depression of the respiratory and cardiovascular systems It is desirable to utilize agents which will maintain a fairly steady depth of sedation and a large degree of flexibility because the pathway between life endangering spasm and serious depression of vital functions is frequently narrow Solution of tribromethanol (avertin) has proved quite satisfactory when used in small amounts frequently repeated Usually a fairly large initial dose is required followed by smaller maintenance doses According to the severity of the disease the initial dose may be 30 to 90 mg per kilogram of body weight and the maintenance doses 10 to 30 mg per kilogram Sometimes difficulty is encountered because the solution is expelled from the rectum Usually this is due to inadequate relaxation either because no sedation has been given previously or because the interval between doses has been too long The administration of sodium amytal intramuscu

tion of tribromethanol may be used Considerable caution must be exercised in giving sedatives intravenously to patients with tetanus lest in one s haste to control a severe spasm an amount of the sedative be given which proves to be dangerously depressing once relaxation occurs The use of dilute solutions injected slowly will diminish this hazard In some cases of severe tetanus sodium amytal may be needed to supplement the rectal medication especially at times when severe spasms might be precipitated by necessary manipulations of the patient Capsules of seconal 100 to 500 mg at a time inserted into the rectum are a practical means of sedation in the milder cases or during the recovery period of more severe cases Careful charting of the amounts of sedatives totaled every 12 hours and notes as to the reaction of the patient afford the best guide as to the maintenance dosage of sedatives required

Severe pain and great terror are engendered by the spasms of tetanus These can be relieved by sedation in mild and moderately severe cases Painful spasms cannot be safely eliminated at all times in severe cases In such instances small to moderate doses of an analgesic such as 0 6 gm of aspirin may greatly aid in the management of the patient Demerol hydrochloride 100 mg with less respiratory depressant action may be preferable to morphine although the latter has been used successfully in many cases

The parenteral administration of magnesium sulfate has numerous advocates but with this drug the relief of spasms has [illegible] definite whereas alarming d

sion of respirations has been noted quite frequently

Curare has been suggested as an ideal agent for relieving the spasms of tetanus When proper dosages and precautions have been determined this drug may have considerable value in tetanus but the evidence to date does not warrant its use except on an experimental basis by those experienced in its administration The use of d tubocurarine in peanut oil and beeswax has diminished the need for frequently repeated doses However in many cases the amount of curare required to control convulsions has dangerously depressed respirations Bronchospasm secondary to the action of curare in liberating histamine in unanesthetized patients may be expected in some patients Until the mechanism of the lethal effect of prolonged curarization observed in dogs has been explained its use in full doses over long periods of time cannot be recommended in cases of tetanus

Cyanosis in a patient with tetanus may be due to a variety of conditions such as the accumulation of secretions in the pharynx spasms of the glottis or respiratory muscles excessive depression of the respiratory center or as the result of atelectasis or pneumonia Placing the patient on his side or face down with the head low with or without gentle mechanical aspiration will relieve the first condition Readjustment of the level of sedation will generally relieve the second and third conditions When laryngeal and pharyngeal spasms are interfering with the passage of air a tracheotomy should be performed Oxygen should be on hand at all times and should be given to any patient with cyanosis

Satisfactory hydration of the patient during the period when oral fluids cannot be taken with safety may be accomplished by means of 5 or 10 per cent glucose in water and physiologic saline To cover the obligatory losses of water from the lungs and skin and provide water for urine formation glucose in water should be given 125 cc per kilogram of body weight per day for an infant and gradually decreasing amounts for older children down to 30 cc per kilogram per day for an adult Sufficient sodium and chloride will be provided by a total of 75 cc of saline for infants and up to 250 cc for adults each day unless there is an unusu large amount of perspiration The tende is to give excessive amounts of sodium chloride to patients with tetanus Daily b

to guide the fluid therapy

When food can be taken by mouth safe a liquid high carbohydrate adequate calo diet may be offered Otherwise during critical period of the first five to seven da the potential danger of tube feeding or an extensive program of intravenous fe ing overshadows any benefit to the patie Patients with tetanus maintained free fr serious spasms well oxygenated and in go hydration readily tolerate the necessary gree of partial starvation whereas fa spasms have resulted from injudicious tempts to maintain caloric equilibrium

Urinary retention especially in adults m require catheterization of the bladder If it should be done during the time wh sedation is deep

Competent nursing supervision is inval able in the maintenance of a more or le heavily sedated patient with a minimum disturbance As long as serious spasms occ no patient should be left alone

Preventing Additional Toxin fro Reaching the Central Nervous Syster The results in many thousands of injure patients have conclusively demonstrated t efficacy of prophylaxis by means of adequa passive immunization If these observation are accepted it follows that tetanus ant tox alone in sufficient quantity will prevent tox as yet unbound from reaching the centr nervous system The corollary is that othe measures designed to prevent the spread tetanus toxin from its site of elaborat on ar

should be gauged by the severity of the di ease as indicated by the length of the incu

sodes of generalized muscle spasms occurred Size of the patient should not be used t calculate the amount of antitoxin In occa

sional severe cases up to 1 000 000 units of antitoxin may be needed

All too frequently serious reactions follow the administration of tetanus antitoxin espe cially in children The intramuscular route is the safest one for the administration of the serum but because the time factor may be important especially in severe cases one half of the antitoxin may be given intra venously to such patients Mild cases or patients believed to be sensitive to the serum used should not receive antitoxin in travenously Although the administration of antitoxin intrathecally provides some addi tional protection to experimental animals there is merely suggestive evidence of its usefulness in human patients with tetanus Intrathecal administration of tetanus anti toxin has caused death in some patients who in all likelihood would have survived their tetanus infections Therefore if the intra thecal route is used at all it should be re served for only the most severe infections

Reactions to serum will be minimized by using highly purified concentrated serum carefully administered Individuals sensitive to serum may be detected from a history of previous administration of serum to the pa tient or of allergic manifestations in the patient or his family The ophthalmic test for sensitivity and an injection of solution of epinephrine hydrochloride (0 1 cc for in fants to 0 5 cc for adults) with or without atropine (0 1 to 0 6 mg) probably should be used prior to serum administration Be fore a large amount of serum is given intra venously it is desirable to inject only 0 5 cc of a 1 10 dilution of the serum intravenously and to check the clinical condition of the patient and record his blood pressure for 20 m nutes before proceeding For the early de tection of thermal reactions the patient s *temperature should be taken every 30 min* utes for the first 3 hours after serum ad ministration

Surgical Procedures and Chemotherapy The proper surgical care of injuries irrespec tive of the presence of tetanus is essential when the nature of the injury is such as to require operative intervention but only those surgical procedures which would be recom mended in the absence of tetanus should be performed An operation for the sole pur pose of removing the presumed focus from which toxin is being elaborated is unneces sary in the presence of circulating antitoxin as has been demonstrated by both experi mental and clinical observations

The use of penicillin solely for its action on the tetanus bacilli is likewise unnecessary and is undesirably disturbing to the patient

The use of phenol parenterally for its sup posed detoxifying action as recommended by F

cisc

uns

tetanus

Pneumonia This is still a serious compli cation of tetanus despite the availability of chemotherapeutic agents The inciting fac tors of hypostasis and inadequate pulmonary excursions can be diminished by frequently changing the patient s position and by using sufficient sedation to prevent rigidity of the thoracic cage and by avoiding undue depres sion of respirations from excessive sedation Periodic inhalations of oxygen with 10 per cent carbon dioxide may be used if well tolerated It is probably better to reserve the use of sulfonamides and penicillin for treat ment of pneumonia if it develops rather

After Care Two points in the manage ment of patients recovering from tetanus deserve mention The first is that all patients even those with mild tetanus should have a roentgen examination of the spine before being discharged from the hospital in order to detect compression fractures of the verte brae The second is that all patients who have received antitoxin should subsequently be actively immunized against tetanus inas

render a second use of serum more dan gerous

Prophylaxis Study of the nature of the injuries resulting in tetanus in civilian life reveals that only a program of active im munization which will produce and con stantly maintain a high level of immunity will prevent this disease All cases of tetanus cannot be prevented by reliance on immedi ate surgical treatment of injuries nor by pas sive immunization with antitoxin nor by the

type of active immunization which depends upon the use of "booster" doses of toxoid at the time of injury, even though each of these measures is effective when applied. Many cases of tetanus occurred either when no injury was recognized or when the injury was so trivial that these methods of preventing tetanus would not ordinarily be utilized. The remarkable success in protecting military personnel from this disease has unequivocally demonstrated that active immunization against tetanus is one of the most worthwhile measures in preventive medicine.

Active immunization is especially recommended for children, farmers and artisans. It is particularly important to immunize actively persons naturally allergic to horse serum or who have received horse serum therapeutically. The favorable publicity given immunization procedures during recent years should be utilized to promote this effective preventive measure.

For children and adults three injections of 1 cc of fluid toxoid given at 1 to 3 months intervals and followed by restimulating injections of 0.5 to 1 cc of toxoid every 2 years is the most widely recommended program.

For primary immunization in infants most workers agree that alum precipitated or aluminum hydroxide adsorbed tetanus toxoids combined with diphtheria toxoid and maybe also phase I *Hemophilus pertussis* vaccine is the preparation of choice for basic immunization. If combined diphtheria tetanus alum precipitated or aluminum hydroxide adsorbed toxoids are used 1 cc of the preparation is given when the patient is 5 to 6 months old and again 3 months later, and after another 3 months 1 cc of tetanus toxoid alone is given. Combined vaccines employed during the first quarter of the first year are producing favorable immunization responses and may become the recommended basic immunization procedure after more clinical trials. One year after the basic immunization 0.5 cc of alum precipitated or aluminum hydroxide-adsorbed tetanus toxoid should be injected and repeated every 2 years.

Although basic immunization followed by restimulating injections every 2 years provides adequate immunity in nearly all cases, caution dictates that a booster dose of fluid tetanus toxoid be given whenever an injury from which tetanus is particularly prone to develop is sustained.

Although prophylaxis with tetanus antitoxin cannot prevent all cases of tetanus when properly utilized its efficacy is unequivocal. It is obvious that passive immunization should be used whenever a patient not actively immunized presents himself for treatment of an injury recognized as a potential source of tetanus. Since 1500 American units of antitoxin have been inadequate occasionally, at least 5000 units should be used. For extensive injuries with a great deal of devitalized tissue or if a considerable period of time has elapsed between the injury and the prophylactic treatment two to four times that amount of antitoxin should be given.

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ANTHRAX

The results of modern therapy can best be appreciated from the figures collected by Smyth. In 25 cases with no treatment because of wrong diagnosis the fatality rate

was 88 per cent while in 749 treated cases the death rate was 7 4 per cent With the advent of the antibiotics there is hope for further reduction in the mortality rate from anthrax Two series of penicillin treated cases have already been reported with no deaths by Ellingson and his associates and Griffith and his co workers In our last 78 cases we had no fatalities

Cutaneous Anthrax This should no longer be considered a surgical problem There is no justification for incision excision or cautery of the skin lesion Local treatment should consist of rest of the affected part by

control secondary pyogenic infection of the ulcer as indicated Systemic treatment should be started as soon as the disease is suspected and should not await bacteriologic confirmation but smears and culture of the region should always be taken prior to therapy The results are definitely influenced by the early recognition of the disease and the institution of prompt and adequate treatment This may consist of (1) antibiotics (2) sulfonamides (3) neoarsphenamine (4) antianthrax serum (5) miscellaneous

Treatment should be continued until the edema has cleared cultures from the lesion have become negative for B *anthracis* and signs of toxicity fever rapid pulse malaise have subsided Judged by the rapidity with which these criteria are met penicillin is the drug of choice However it must be noted that the course of development of the "pustule" through the stages of papule vesicle and eschar formation is not affected by any form of treatment regional adenopathy may persist after healing of the ulcer has set in and the patient is well on the road to recovery

Penicillin Both in vitro and animal experiments have conclusively shown that B *anthracis* is sensitive to penicillin but the degree of sensitivity varies with different strains Furthermore the in vitro sensitivity

cultures with 60 000 units of penicillin intramuscularly in each of five doses followed by 30 000 units every 3 hours by the same route Their total dosage ranged from approximately 1 000 000 to over 4 000 000 units All patients recovered Previously Murphy et al reported studies on 3 cases and found that a total of 100 000 units of penicillin is certainly the minimal effective dose in the uncomplicated case of cutaneous anthrax They concluded that at least a total of 200 000 to 400 000 units of penicillin given at the rate of 100 000 units per day should be administered to the average adult and this amount should effect a prompt and satisfactory therapeutic response Similar results were reported by Stott Weinstein and Oliver Mann and Griffin et al treated 17 cases with 100 000 to 300 000 units of penicillin every 3 hours intramuscularly with a total average of 12 882 940 units during the hospital course All face and head lesions also received sulfadiazine One case of meningitis was supplemented with antianthrax serum The authors felt that because of the scarcity of reported cases it was safer to administer large doses of penicillin

We prefer to give a large initial dose of 100 000 units of penicillin intramuscularly followed by 20 000 to 50 000 units every 3 to 4 hours depending on the severity of the case As soon as the edema recedes (24 to 72 hours after penicillin therapy is begun) the dosage is decreased to about 20 000 units every 4 hours this is then continued for a day or two In the early part of treatment an occasional patient may show increase in the erythema and swelling around the lesion This however subsides within 24 hours Adenopathy may persist for a few days or weeks after the patient is otherwise well its presence is no indication for continued therapy We recently treated a case of anthrax of the face with procaine penicillin in oil A single daily injection of 600 000 units was

tory care is possible

Streptomycin In experimental infections of mice Miller et al found streptomycin to be highly effective in doses of 800 to 1600 units daily per 18 to 22 gm of mouse This is within the limits of maximal dosage in man Also Housewright et al confirmed in anthrax infections in mice the reported addi

tive effect in vivo of streptomycin and penicillin No clinical studies have as yet appeared on human infections treated with streptomycin Although the Council on Pharmacy and Chemistry in its report on this antibiotic stated that "It is occasionally effective in anthrax," it is likely, in view of the animal experiments, that streptomycin will be of value if given in doses of 1 to 2 gm daily However, the greater risk of toxic reactions and its relative expensiveness makes this drug quite inferior to penicillin

AUREOMYCIN This new antibiotic has been tried by the writer in a case of anthrax of the wrist with satisfactory results The edema erythema and signs of toxicity were controlled within 48 hours after therapy was instituted but bacteriologic control was not achieved until the fourth day As expected the "pustule was not affected in its course of development This patient received 0 75 gm of aureomycin orally every 4 hours until the edema began to recede, thereafter, the dose was reduced to 0 5 gm every 6 hours

In vitro tests showed that *Bacillus anthracis* recovered from the lesion was sensitive to aureomycin, growth being inhibited by 0 025 microgram per cubic centimeter Its ease of administration, absence of reactions, and the fact that it allows for ambulatory management of cases of anthrax makes aureomycin a welcome addition to our therapeutic armamentarium

SULFONAMIDES Both experimental and clinical studies confirm the value of sulfa ... the treatment of an

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quate blood levels, the drug is given orally for 2 or 3 days Alkalinization and adequate urinary output are secured and frequent urinalysis and blood counts are done If the edema is not controlled by the third day, a change in therapy is indicated Until the advent of penicillin, we preferred the sulfonamides for the treatment of cutaneous anthrax even though their effect on anthrax edema was not as prompt as that produced by optimal doses of antianthrax serum The morbidity rate was definitely decreased, the cost per patient was lowered and ambulatory care was possible

NEOARSPHENAMINE In our hands, the sulfonamides were found to be superior to neoarsphenamine The latter drug was given by us in addition to antianthrax serum to a group of 10 patients without any effect upon the course of the disease or its morbidity Similar findings were reported by others However, Lucchesi and Gildersleeve definitely expressed a preference for neoarsphenamine and recommended an initial dose of 0 6 gm followed by 0 9 gm on each of 2 suc

no deaths

ANTIANTHRAX SERUM Following the demonstration of the therapeutic value of penicillin and sulfonamides the use of specific serum has been practically abandoned Most pharmaceutical firms have ceased to manufacture it, yet occasionally one encounters a virulent infection which resists all forms of available therapy and under such circumstances, one wishes for a potent horse serum

When used it should be given in large amounts to secure optimal results An initial dose of 300 to 500 cc intravenously, repeated in 12 to 24 hours, may be needed to control the spread of the edema Thermal and sensitization reactions and serum sickness are frequent complications following its use

MISCELLANEOUS Local applications of small doses of roentgen rays immunotransfusion, ordinary horse serum injections, etc have all been used in the treatment of anthrax with debatable or indifferent results It is obvious that supportive treatment and good nursing care are required in this as well as in any other disease

Internal Anthrax In this country, internal anthrax is rather infrequent We have seen only one case of pulmonary anthrax Bacteremia with secondary localization in the lungs and meninges has been reported by Lucchesi and Gildersleeve, Weinstein and Oliver, and Shanahan et al In the presence of anthrax pneumonia or systemic invasion much larger doses of penicillin than those recommended for the cutaneous form should be used In addition, sulfadiazine should be administered by mouth or intravenously In meningitis, the intrathecal injection of penicillin, 20 000 to 30 000 units repeated if necessary every 12 to 24 hours, is indicated, in addition to parenteral therapy Proper

precautions should be used to avoid untoward reactions and cross infection of the cerebrospinal system

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GLANDERS

Glanders in man as in equine animals varies from an acute fulminating infection with septicemia to a chronic debilitating process with multiple lesions in the skin and viscera The acute fulminating form has seldom been diagnosed before death and treatment has been symptomatic and ineffective Treatment has been more successful in milder acute forms and in chronic glanders

Sulfadiazine is reported to be the most effective of the chemotherapeutic drugs in in vitro and in vivo tests Fifty per cent of animals recovered when treated for 7 days and 100 per cent recovered when therapy was continued for 20 days Sulfathiazole sulfamerazine and sulfanilamide are somewhat less effective in vitro and have not been [illegible]

[illegible] against a subacute form of the disease in man Streptomycin, although moderately effective in vitro, had no effect on the experimental disease in hamsters

In 6 cases of acute human glanders occurring in laboratory personnel, recovery took place after treatment with sulfadiazine It is felt that the most effective therapeutic regime is as follows As soon as blood culture or serologic tests indicate a diagnosis of glanders, the patient is given 5 gm of sodium [illegible]

forced fluid intake aid in reducing drug complications The strong tendency of the disease to form latent foci of infection which later become reactivated is best combated by administering intensive and uninterrupted therapy early in the course of the disease Complete bed rest during therapy and a prolonged convalescent period permitting only light activity are important adjuncts A well balanced diet with supplementary vitamins should be maintained during the acute illness and through the prolonged convalescence for maximum promotion of healing The patient should be examined monthly for at least a year after apparent recovery The development of a temperature elevation skin pustules, localized chronic lymphadenitis, hepatomegaly or splenomegaly,

patchy pneumonic infiltration, or a sudden rise or precipitous fall in serum antibody titer indicates a probable recurrence of the disease in a subacute or chronic form

Chronic glanders is resistant to all forms of therapy Although the mortality rate is high, a small percentage of patients have recovered after a long illness Cox Bristow, and White have made reports which claim benefit from the use of autogenous vaccines, and Watson from "immune serum, mallein, heavy metals, iodides, and quinine The value of these methods has never been con vincingly demonstrated Many cases were treated surgically with multiple incisions of the abscesses and sinuses, and excision or amputation of infected areas but with no lasting benefit No reports have been found of treatment of chronic glanders with sulfa diazine Treatment of chronic experimental glanders with sulfadiazine for 20 days re sulted in a remission of the infection during therapy, but in the majority of the animals a fatal relapse occurred weeks or months after therapy was discontinued

Chronic glanders would probably best be treated with a long period of complete bed rest as in tuberculosis and a course of sulfa diazine therapy continued for 2 to 3 months if the drug can be tolerated Since it has been shown that Malleomyces organisms in vitro develop sulfadiazine resistance rather easily, administration of the drug in small doses or in intermittent courses should be avoided whenever possible Surgical drain age of fluctuant abscesses is always indi cated Wide excision or amputation of in fected parts may give temporary benefit but is chiefly a palliative measure since foci of infection are widespread Although anti bodies can be demonstrated in chronic glanders and in vaccinated animals by ag glutination, precipitation, and complement fixation technics, attempts to demonstrate a definite active or passive immunity have been unsuccessful Autogenous vaccines and antisera may be tried as adjuncts of therapy but are of doubtful benefit A state of hyper sensitivity in glanders can be demonstrated by a tuberculin like skin reaction to mallein Reports of benefit by desensitization ther apy, however, have never been confirmed Three to 5 gm of sodium or potassium iodide by intravenous or oral routes may be ex- pected to be of some benefit in aiding reso lution of the semicaseous or suppurative lesions Prolonged rest, adequate fluid bal ance, a well balanced diet with supple mentary vitamins, and other general supportive measures are important as in any chronic disease Patients with apparent clini cal recovery must be followed carefully for 1 or 2 years for signs of relapse

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be useful in glanders

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MELIOIDOSIS

The recent report by McDonald and Var ney of a case of chronic melioidosis in this country has aroused interest in a disease which formerly had been contracted only in southeastern Asia The more common acute septicemic form of the disease is rapidly fatal and seldom diagnosed before death There are no reports of treatment of this form of the disease with sulfonamides Recovery oc curred in 2 cases of subacute melioidosis seen by Harris et al, limited to the respira tory tract after a total of 23 days' treatment with sulfathiazole and/or sulfamezathine In several cases of chronic melioidosis a remis sion occurred during 10 to 15 day courses of sufadiazine, sulfathiazole, or sulfamethazine, but all relapsed after therapy was discon tinued, according to Harris et al and Grant and Barwell

Sulfadiazine is effective against the acute experimental disease in hamsters When treatment was continued for 21 days 100 per

cent of the animals recovered Penicillin has been shown to be completely ineffective against *Malleomyces pseudomallei* in vitro against acute experimental melioidosis in hamsters and against acute and chronic melioidosis in man as reported by the authorities in the References Streptomycin showed a transient bactericidal effect in vitro but was ineffective in treatment of the acute experimental disease and in the chronic disease in man

It is felt that sulfadiazine will give marked benefit in acute human melioidosis if treatment is instituted early As soon as the disease is suspected 5 gm of sodium sulfadiazine should be given intravenously fol

4 hours and a forced fluid intake aid in reducing urinary drug complications Continued signs of active infection during therapy indicate a shift to a subacute or chronic form of the disease and treatment should be prolonged accordingly

Chronic melioidosis like chronic glanders is characterized by multiple lesions in the skin and viscera which vary from tiny granulomas to pyogenic abscesses and draining sinuses To be of maximal benefit sulfadiazine should therefore be administered in full therapeutic dosage for long periods It is felt that the patient should be kept at absolute bed rest and given sulfadiazine in 1 gm doses every 4 hours for 2 to 3 months or until severe drug toxicity develops In a disease which is 95 per cent fatal a mild or moderate degree of drug intoxication need not require cessation of therapy Intermittent therapy or treatment with small dosage tends to encourage development of drug resistant strains The best possibility of recovery depends on early diagnosis and

be given every 4 hours with a forced fluid intake Three to 5 gm of sodium or potassium iodide daily given intravenously or by mouth aid resolution of the semigranulomatous or suppurative lesions Antisera autogenous vaccines or whitmorine may be tried as an adjunct of treatment but are of doubtful value Incision of localized abscesses and obstructed sinus tracts is indicated to establish drainage Wide excision cauterization or amputation of infected areas may be temporarily beneficial but do not result in cure Cases of apparent recovery should be examined frequently since relapse may occur as long as 1 or 2 years later

The efficacy of aureomycin against many gram negative organisms offers hope that it may be beneficial in melioidosis

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TUBERCULOSIS

Medicine is half a science and half an art The term "science" implies change and an "art" is something that is done differently by each practitioner At the present time the science of medicine is advancing with extreme rapidity and in the treatment of tuberculosis a disease of great variety in which psychologic social and economic factors play an important part the element of art is great Each physician has prejudices and preferences which are the result of his particular experience and his personal evaluation of almost inevaluable factors For the first reason every textbook on medicine is certain to be out of date by the time it is published and for the second reason every textbook on tuberculosis is bound to be an expression of only one of many points of view Whoever reads a textbook should remember that the science has advanced since the text was prepared and that the art is personal and must be learned by long experience

The Types of Treatment Pulmonary tuberculosis has been known and recognized

since the earliest times and thousands of medicines and regimens have been recommended for its treatment The failure of all remedies stimulated the quest for new ones, and throughout the centuries, in steady succession, everything from drinking goat's milk or ox blood to residing in this or that particular climate was heralded as a cure In spite of this, until less than 90 years ago the disease was considered regularly fatal and physicians prescribed and patients tried this or that treatment desperately and hopelessly Hippocrates prescribed mountain air and Galen sent his patients to drink goat's milk at his farm on the hills above the Bay of Naples When Keats spat blood he was advised to take a walking trip in Scotland Chopin was told to go to the Island of Minorca and Laennec following Galen, took himself to the coast, where, as he walked by the sea and subsisted upon goat's milk, he watched the progression of the physical signs in his own chest

Since 1868 when Bremer and Deitweiter first demonstrated the efficacy of rest in bed, three true remedies have been found These are rest in bed, collapse or excision of the affected portions of the lungs, and, recently, streptomycin Of all the thousands of measures which have been suggested and tried those are the only three which have been proved to have any value The laity and some of the medical profession still have faith in particular climates and some patients still insist on having goat's milk but most now recognize that a well balanced general diet is all that is important and that any climate is satisfactory save a tropical one in which excessive heat and humidity render existence, even of the well, difficult and precarious Patients will recover equally well and quickly in all temperate climates and at all altitudes and on any adequate and well balanced diet They will not recover at all save rarely and by chance, without bed rest, or bed rest and streptomycin, or bed rest, streptomycin, and collapse or excision

Bed Rest Rest in bed is effective in the treatment of pulmonary tuberculosis chiefly because it decreases the motion of the lungs It favors, as does the rest of any infected part, the localization and control of the infection and the repair of the injury to tissue In the lungs also it discourages the aspiration of infected secretions into unaffected pulmonary areas

Rest in bed decreases the motion of the whole of the lungs by approximately 75 per cent and of the parts affected by disease by a still larger amount. The movement of the lungs is in proportion to the oxygen requirements of the body, and at complete rest these are not more than one fourth of what they are under full body activity

Rest in bed is selective for the diseased portions of the lungs because these are less elastic and therefore less easily moved than the normal parts If the lungs are being used little diseased areas move even less and it is only when motion is exaggerated that they are brought into full play Rest in bed may be made still further selective by having the patient lie on the affected side or by applying a splint to one half of his chest or by having him hold a shot bag over the affected portion

Recently evidence has been offered that the blood supply to the upper parts of the lungs is appreciably reduced when an individual is in the upright position This has been advanced as the reason for the preference of tuberculosis for the apices, and it has therefore been suggested that the recumbent position, by increasing the flow of blood to the affected areas, favors healing

The patient's position in bed is important for other reasons Postural drainage, which is desirable in lung abscess and bronchiectasis, is dangerous in tuberculosis because it favors the spill of infected secretions into the unaffected lung areas which in postural drainage are usually made dependent For this reason the patient with tuberculosis should be cautioned against lying on his better lung The advantages of better drainage are much less than the danger of spread of the disease

Rest in bed is effective in proportion to bodily activity Some patients can be very active in bed Many cautious phthisiologists insist that patients with acute tuberculosis ... that they even

sobbing cause excessive motion of the lungs For this reason temperatures are always higher on visiting days and for this reason patients with acute disease should always be in private rooms A good spell of sobbing

such as women frequently indulge in is extremely dangerous and is often followed by an exacerbation or spread of the disease

Part of the value of sanatorium care and rest in bed is the regularity of the life The body at the autonomic level is greatly affected by habit An individual eats digests excretes rests and sleeps best if he does these things at the same time each day For this reason patients should be upon a rigid [illegible]

schedule for a few weeks he follows it out of desire—he relaxes into it as it were and mentally and physically exists with much less effort and with much greater efficiency At certain times of the day his whole body becomes ready and eager for food or rest or sleep and what has become habitual becomes easy and desirable

Rest in bed is still the basis of all treatment of pulmonary tuberculosis It should precede accompany and follow all measures of collapse or excision It is the only treatment which affects all of the foci of tuberculosis in both lungs equally and only after the disease has been rendered quiescent by rest are the other measures apt to be successful and uncomplicated It should be complete and should be persisted in in curable cases as long as the sputum is positive simply because bodily activity favors exacerbation and extension

Rest in bed should be complete in proportion to the acuteness of the disease Truly acute exudative and febrile cases should be on absolute bed rest in private rooms As the acute stage passes they may tolerate complete rest in a double room or a ward and later may be allowed bathroom privileges but in all cases while bed rest is being used these should be the limit of privileges granted until the lesions are closed and the sputum negative

The improvement from bed rest decreases steadily with time It is greatest in the first month less in the second still less in the third etc Maximal benefit has usually been obtained in from 4 to 8 months From this time on cavities rarely decrease in size and cure from simple rest rarely occurs The time has come then to resort to whatever measure of collapse seems indicated

Rest in bed should be in a sanatorium Only there where all are on the same regimen can discipline be enforced and only there can the patient be under the close observation of the physician who must study and observe him from week to week and month to month so that he may be able to vary the treatment as indicated and apply collapse when that becomes advisable or necessary And only in a sanatorium can a patient absorb an understanding of the seriousness of the disease with which he is afflicted and the measures which are necessary for recovery

It is important that those with small lesions see people coming back with recurrences that they see some die of tuberculosis and others undergoing serious operations

Most individuals and some inexperienced physicians believe that patients will rest as well at home as in a sanatorium The patient who will do so is extremely rare Strict bed rest is bitter medicine to take and the individual who will discipline himself to it at home is extremely rare The physician's first function therefore is to convince the patient that he must go to a sanatorium and in nearly every case he must do this against the patient s strong desire and his many arguments and objections But unless the physician succeeds in this first step he is apt to fail in his entire purpose

Collapse Therapy In 1822 James Carson an English physician pathologist and physiologist made the statement that if certain types of pulmonary tuberculosis were ever to be cured it would be by collapsing the diseased lung Carson was the first to measure the intrapleural pressure He reached his conclusion concerning tuberculosis from his realization that the lungs were continually stretched to fill the thorax and from his observation in performing necropsies that the chief obstacles to the healing of tuberculosis were the cavities which were prevented from closing by the stretching of the lungs He suggested both artificial pneumothorax and thoracoplasty and although it was 60 years before collapse was applied clinically, his article foreshadowed the second great advance in the treatment of tuberculosis

Between 1882, when Forlanini first used artificial pneumothorax, and the present time not only have pneumothorax and

thoracoplasty been perfected but also artificial paralysis of the diaphragm extrapleural pneumonolysis internal pneumonolysis pneumoperitoneum and Monaldi s drainage Each of these methods of collapsing and resting the lung and closing cavities has proved to be a valuable addition to the armamentarium Each has its particular uses and all together combined with bed rest and more lately with streptomycin have made it possible to cure or bring under control all save the most advanced cases of pulmonary tuberculosis In *considering them it is im*portant to bear in mind that their great function is solving the major problem in the treatment of tuberculosis the closure of cavities

Collapse of the lung sufficient to close all cavities is a specific remedy for tuberculosis The local rest and the approximation of the walls of the cavities will produce arrest of the disease in practically every case In a text concerned only with treatment this statement is sufficient It is not necessary to consider *the precise reasons for the effect* It is necessary to consider the particular advantages and disadvantages of each form of collapse and the particular indications for its use

The Indications for Collapse Therapy In general the methods for collapsing and resting the lung may be divided into two classes i e those which are so simple and safe that they may be used early to hasten and assure recovery and those major surgical procedures which probably should be used *only* when all other methods of treatment have failed and permanent collapse is absolutely necessary In the first group are phrenic nerve operations artificial pneumothorax and pneumoperitoneum and in the *second are thoracoplasty* extrapleural pneumonolysis and Monaldi s drainage Excision will be considered under a separate heading

In the treatment of tuberculosis and in the application of collapse measures there are many *matters which are* and *always* will be controversial Where there are so many possible sequences and combinations of treatments where judgments based on accurate statistics are so difficult to secure and the factors to be balanced *against each other* are so often in different categories it is impossible for all to agree and it is not good *that they should* It will always be difficult to decide whether in any particular case the risks incident to artificial pneumothorax are preferable to a year or two of invalidism or whether the extended slight hazards of "air" are preferable to the definitive collapse of a thoracoplasty which carries with it the permanent *psychologic handicap of an irre*versible alteration in the shape of the body In the long run each man on the basis of his own experience and his human understanding of each particular patient must *make his own decisions* and mix and apply his treatments to accomplish the desired result in consideration of the particular type and extent of the disease in the particular patient

Phrenic Nerve Operations Induced paralysis of one half of the diaphragm is the simplest and *safest* of all *collapse measures* If it is at all indicated there is no good reason for not using it The only contraindication is a situation where the reduction in vital capacity would eventually interfere *with some more effective type of collapse*

While it is the least drastic of all collapse measures it is also the least likely to be [illegible] combina [illegible] results [illegible] cases it seems to have little effect and in others it is followed by the rapid closing of cavities The occasional dramatic results and the probability that in every case it at least favors the closure of cavities are good *reasons for using* it quite generally

The effectiveness of phrenic nerve block varies with the location of the lesions in the lung One would expect it *to give the best* results in lesions in the base For some *reason* concerned probably with the evacuation of secretions this is not so and these lesions are the ones least likely to be favorably influenced It has more chance of closing infraclavicular cavities and is almost *specific for* those close to the hilus and particularly for those posterior to the hilus in the apex of the lower lobe

For unilateral or chiefly unilateral disease it is reasonable to *block* the *phrenic nerve* at the start of treatment in addition to the bed rest and streptomycin therapy One can feel confident that it will do no harm in some cases the result will be dramatic, and in every

case it will favor the closure or the reduction in size of cavities

If phrenic nerve block is followed by closure of cavities and arrest of the disease it should be repeated each 6 or 8 months for a year or two or should be made permanent Prior to 1935 all phrenic nerve operations either severed or extracted the nerve Many of these patients have remained well and almost none has experienced any permanent inconvenience

Phrenic nerve block has been advocated in conjunction with artificial pneumothorax The adherents of this practice believe that it reduces the respiratory pressure changes in the pneumothorax space increases the interval between refills and in general aids appreciably in the rest and relaxation of the lung

Blocking the phrenic nerve at the end of a course of pneumothorax is a reasonable procedure It favors the re expansion of the lung and decreases the tension which will be exerted on the diseased areas Immediate recurrences are less likely and less common if this is done

If the phrenic nerve is blocked when an unsuccessful pneumothorax is abandoned the results are often dramatic A cavity which has remained suspended for many months may suddenly close Why this is so is uncertain It is certain that it happens so often that it cannot be explained as mere chance The procedure is always worth trying

PNEUMOPERITONEUM The injection of air into the peritoneal cavity elevates the diaphragm and relaxes the lungs If one half of the diaphragm has been paralyzed it greatly exaggerates the effect of this operation It has the great advantage of being almost completely safe and of having few complications The only good reason for not using it early in any case in which it is at all indicated is that its value is still questionable and that it commits one to a course of treatment which one may feel impelled to continue for a long period

The results of pneumoperitoneum are not as dramatically demonstrable as are those of pneumothorax and thoracoplasty The procedure is an adjunct to complete bed rest and its effects are gradual and difficult to distinguish from those caused by rest and streptomycin For this reason its position in the armamentarium is still a matter of controversy It has its enthusiastic adherents who prefer it to pneumothorax and its doubters and detractors who do not use it at all If it lacks the complications of pneumothorax it also lacks its great effectiveness in hastening and assuring recovery It seems definitely indicated in far advanced bilateral disease in which pneumothorax is impossible It may possibly be of much wider value when used early in many other cases in which like phrenic nerve block it may, with bed rest and streptomycin aid in the closing of cavities which would not close without it In this manner alone it is conceivable that in many cases it can prevent the ultimate necessity for major surgical collapse

ARTIFICIAL PNEUMOTHORAX Artificial pneumothorax the first of all the collapse measures to be developed and perfected is still the most effective and the most widely applicable The direct and variable collapse which it produces closes cavities quickly and completely and puts the diseased portions of the lungs at almost complete rest It converts the sputum quickly and does hasten and assure recovery In most cases and in many others to a large extent it is reversible A person with one or both lungs well collapsed by pneumothorax can return to work and to normal function much earlier and can continue relatively strenuous activities much more safely than one who has recovered on rest or phrenic nerve block or pneumoperitoneum

This is the bright side of pneumothorax The dark side is provided by the pleurisies which often complicate it These vary from small asymptomatic accumulations of fluid through acute transient tuberculous infections to tuberculous empyema or mixed infection empyema or most serious of all to empyema with bronchial fistula The least of these produce some slight thickening of the visceral pleura which does not interfere with eventual complete re expansion of the lung The important ones partially compromise re-expansion and the truly serious ones prevent it and lead to the necessity for extensive thoracoplastics decortications or pneumonectomies Fortunately, the serious complications are rare and are usually in proportion to the extent of the original dis

ease Today with the use of antibiotics it is possible to meet and overcome most of the complications without resorting to major surgery

One can say therefore that artificial pneumothorax may be used as an elective procedure in minor cases which might occur without it if the temperament of the patient is such that he will not submit to rest or if his economic and social situation demand an early return to a strenuous life In cases which require major collapse it is the most effective and the least serious and should therefore be tried before attempting major surgery

In the treatment of a disease as threatening and incapacitating as tuberculosis the slight risks incident to treatment with pneumothorax are worth running It is important in that it permits young women to marry and have children and young men to proceed with their strenuous careers

It is difficult to weigh these advantages against the disadvantages and risks The overconfidence which leads some to use pneumothorax early and indiscriminately and to send the patients back to work without an adequate period of bed rest is not justified nor on the other hand is that attitude justified which is so cautious that it subjects patients to years of unnecessary invalidism and sends them back into life so hampered with restrictions that their lives are spoiled *Certainly pneumothorax is sufficiently safe to be used as an elective procedure to enable individuals to resume normal strenuous careers without too long a period* of invalidism

Some phthisiologists prefer thoracoplasty *to artificial pneumothorax* They feel that in the long run it is safer and that strictly unilateral disease extensive enough to re*quire* collapse had best be collapsed permanently

From a statistical point of view this attitude is probably correct Unfortunately tuberculosis occurs in human beings and most of these greatly prefer the inconveniences and slight risks of pneumothorax with its high chances of success to a permanent loss of ribs and irreversible alteration in the body contour

THORACOPLASTY AND EXTRAPLEURAL PNEUMONOLYSIS Thoracoplasty and extrapleural pneumonolysis are the two forms of major surgical collapse Both are excellent operations Each has its advantages and disadvantages and its particular uses and indications Of the two thoracoplasty is the better operation and should be employed in preference to extrapleural pneumonolysis unless there are definite contraindications

drastic and even less permanent reduction in vital capacity As long as the dead space and the foreign body are present they can cause trouble The late complications which are the only drawbacks of this operation are usually bothersome rather than serious Late tuberculous or nontuberculous infection in the space which may occur even after many years can usually be cleared up by aspiration and irrigation and perforation of the lung with expectoration of the foreign body can usually be handled by removing the *foreign body and performing a local thoracoplasty* The complications are however sufficiently frequent and serious to make *thoracoplasty the preferable operation*

The extrapleural operations should be used therefore only when there are definite *contraindications to thoracoplasty* These are age low vital capacity and bilateral involvement which demands or may demand bilateral surgical collapse The extrapleural operations find their greatest use in older individuals with small chronic apical disease and in those with bilateral symmetrical chronic hematogenous tuberculosis

MONALDI'S SUCTION DRAINAGE AND CAVERNOSTOMY When Monaldi first reported his method of the suction drainage of tuberculous cavities most phthisiologists greeted it with a real though guarded enthusiasm The closure of cavities is the chief problem in the treatment of tuberculosis and this seemed a simple way of solving it It does close cavities and if the cavities stayed closed the procedure would be the most important and

the most generally applicable of any in the armamentarium Unfortunately in most in stances they reopen soon after the suction is stopped and the catheter withdrawn Its great uncertainty and the paucity of good permanent results have limited its use to cases in which no other treatment is possible It should be used therefore only when pre vious collapse and low vital capacity abso lutely contraindicate further collapse or resection or as a preliminary procedure to thoracoplasty for extremely large apical cavities

In writing of Monaldi s drainage at the present time one must entertain the possi bility that the parenteral and intracavitary administration of streptomycin may prove to have increased its effectiveness and widened its indications or that if this has not been done by streptomycin it may soon be done by some new and more effective drug The method fails only because the tuberculous infection on the opposed surfaces of the cavity prevent healing adequate to resist the forces tending to reopen the excavation If the infection could be completely overcome the healing would probably be firm and permanent Maurer of Davos has recently reported good results in the closure of early cavities by Monaldi s drainage used in con junction with streptomycin This suggests that the procedure may need to be retried and re evaluated Our results have been more permanent since the advent of strepto mycin and since on discontinuing the suc-tion we have left the tube in place and continued the drainage indefinitely as a cavernostomy We have not retried it on early and less resistant excavations

Cavernostomy has practically the same limitations and the same indications as Monaldi s drainage Its application with skin flap drainage designed to be permanent is a frank admission of its present inadequacy

Lobectomy and Pneumonectomy At the present time lobectomy and pneumonectomy performed for pulmonary tuberculosis are much less safe than the same operations per formed for nontuberculous disease They are also definitely more dangerous than are thoracoplasty and extrapleural pneumonoly sis The dangers are incident to the nature of the tuberculous infection which is rarely limited to one lobe or one lung and which under general anesthesia spreads easily from one lobe to another Streptomycin and the use of bronchial intubation have done much to decrease the dangers of spread dur ing the operation In spite of this at the present time resection is definitely more dangerous than are thoracoplasty or extra pleural pneumonolysis It seems reasonable therefore to resort to resection only in those cases in which collapse has failed or seems extremely likely to fail

Resection is indicated in the following conditions

(1) Bronchial tuberculosis producing im portant narrowing of the bronchus
(2) Extremely large apical cavities
(3) Basal cavities which do not respond to artificial pneumothorax
(4) Excavated tuberculomas
(5) Cavities which remain open after a well performed thoracoplasty

Streptomycin Prior to the development of streptomycin there was no drug which had an appreciable effect upon the tubercu lous infection Many drugs had been tried and some had been heralded and used but after trial and controversy all had been given up as valueless It seemed obvious that when a good drug was found its effects would be so unquestionable that it would be immedi ately acclaimed and generally adopted This was the case with streptomycin In the test tube in experimental animals and finally in human beings afflicted with tuberculosis it was immediately demonstrated to have an inhibitory effect upon the growth and in crease of the tubercle bacillus and upon the development and spread of the tuberculous infection When in November 1946 it be came available for general clinical use it was immediately adopted and no one then or since has questioned its value

The universal agreement concerning its ef fectiveness has not prevailed as to its use Opinion has differed widely over the type of case in which it is indicated and the dose which should be used In the beginning it was necessary to proceed with caution Strep tomycin was known to have some unfavor able side effects and no one was sure that other even more serious ones might not be-come apparent The drug also was in short supply and was accordingly expensive There was not enough available to treat every case

and in public sanatoria there were insufficient funds For these reasons it was necessary to consider the drug as still experimental and also to select patients to whom it should be given To satisfy the general clamor for it it was necessary to emphasize the fact that it was not free from danger and also to state dogmatically that although it was helpful it was indicated only in certain types of cases

In most institutions streptomycin boards were set up to observe the good and bad effects of the drug and to select patients to whom it was to be given The clinical necessity for caution and the economic necessity for distributing a limited supply subtly affected the clinical judgment of the members of the boards both as to dosage and indications with the result that even after the drug in certain doses had been proved not to be dangerous they continued and still continue to insist that it is valuable but should be used only in certain types of cases One cannot escape the suspicion that what they said so often from clinical caution and economic necessity they have now come to believe And in this line it seems quite certain that the dosage will increase the course of treatment lengthen and the indications widen as the price of the drug decreases

The reasons given for the selection of cases are as follows

(1) Streptomycin *is of value only in soft* exudative lesions it is not effective in chronic fibroid lesions

(2) In far advanced and hopeless cases it cannot possibly bring about arrest of the disease

(3) In minimal easily controllable and moderately advanced lesions streptomycin is not necessary and should not be used because it renders the bacilli immune to the drug and will make the drug useless should the disease progress or recur and become more serious

The first reason would be valid if it were true or if any case of tuberculosis were pure in type or if any phthisiologist could classify each case exactly It has been our experience that streptomycin is valuable in chronic tuberculosis that every chronic case has some acute exudative elements and that the rather pernicious type of clinico phthisio pathologist roentgenologist who can look at a roentgenogram and describe the exact type of lesion present—as if he had made a personal tour of the trachea bronchi and alveoli and on the basis of this minute knowledge can tell whether or not streptomycin will be effective—is likely to be wrong The results which can be expected from streptomycin are predictable only within limits Anyone who uses it extensively is being continually surprised by unexpected results and therefore will have to conclude that a certain a priori judgment is impossible One cannot say "Streptomycin will or will not help this case" Only after having used it in that particular case can he say "Streptomycin did or did not benefit it" and even this statement is often uncertain

To refuse to give streptomycin because a case is so far advanced that recovery cannot possibly be accomplished is to assume too much prognostic ability One of the great roles of streptomycin is that of bringing apparently hopeless cases back into the curable group At the Edward Sanatorium before the advent of streptomycin there were approximately 25 deaths each year Since November 1946 this number has been reduced to 7 and this reduction has been chiefly in the group which formerly would have been considered hopeless

To say that streptomycin should not be used for minimal and easily controllable moderately advanced lesions because it renders the bacilli immune to the drug and therefore precludes its use should the disease progress or recur is not reasonable In this group if treatment is adequate the normal recovery rate is approximately 90 per cent With streptomycin it will certainly be higher and the period of rest and the necessity for collapse will be reduced Furthermore it has been our experience that bacilli resistant to a small dose of streptomycin are not resistant to larger doses In less urgent cases the dose should be small enough to obviate any risk of eighth nerve injury and it should be stopped immediately if untoward symptoms appear All things considered it seems best to use the drug in these cases because of the increase in security which it affords and to count on larger doses and the old methods of treatment in the few cases in which the disease recurs

Those who advocate the selection of cases

have overlooked the great importance of

testinal and other forms of extrapulmonary tuberculosis This is one of its major functions These complications, which formerly were prevalent and accountable for many deaths, are now rare If it had no effect upon existing lesions, it would still always be indicated merely to prevent the development of new ones

COMPLICATIONS OF STREPTOMYCIN THERAPY Streptomycin has been used too short a time to permit one to say that all of its complications have been noted Thus far the only serious complication has been permanent injury to the vestibular apparatus and its resultant loss of a sense of equilibrium The original dose of 2 gm a day of the old streptomycin produced temporary dizziness in many patients and permanent dizziness in a few Most of those with permanent eighth nerve damage adjusted well to the loss They developed new ways of maintaining balance and were inconvenienced only when in the dark This readjustment was most rapid and complete in young individuals less rapid and less complete in older ones In general the

nerve is in part a matter of individual sus

and on the rate of excretion Excretion is largely by the kidneys and for this reason extra care in using it is indicated in older individuals and in those with impaired renal function If any kidney damage is suspected and it should be expected in old people, *renal function tests should be run before* administration of the drug and the dose should be regulated according to the results of these and should be checked by determinations of blood concentration If facilities for testing the blood concentration are not available, it is sufficient to watch carefully for complications and to stop the drug or reduce the dose if they appear

Permanent impairment of the sense of equilibrium is nearly always well compensated It is an inconvenience rather than a serious and disabling handicap It is a small price to pay for recovery from miliary tuberculosis or from severe forms of chronic phthisis Any important risk is not worth running in minimal tuberculosis or in the milder forms which are nearly certain to recover without it This statement should not be interpreted as meaning that the drug should not be used in these cases, merely that it should be used in such doses that complications will not develop and that it should be stopped if any do appear

Doses of 0 5 to 1 gm of old streptomycin varied according to body weight and renal function rarely produce any damage to the eighth nerve Dihydrostreptomycin which has only recently appeared on the market, appears to be much less toxic so that doses of 2 3 or even 4 gm a day can be used without danger of nerve injury It is too

not develop suddenly and that if the drug is

the proper dose of streptomycin or the proper interval between doses Opinion on these matters has been somewhat influenced by the

be in proportion to the concentration of the drug that reaches them It is known that different strains of the organism vary in their susceptibility to the drug and that all strains acquire resistance to it We have noted that some cases which fail to improve on 1 gm, improve rapidly when the dose is raised to

There is so much to be learned on the whole subject that at the present time and for some time to come, an expectant open mindedness should be the proper attitude It may be that large doses for a short time are preferable to smaller doses for a long time etc It seems certain that the important factor is the concentration in the blood and the dose should be adjusted to the body weight and to the rate of excretion by the kidneys

No one yet knows how to fit streptomycin into the old formulas of treatment. Over many years phthisiologists have learned by experience how much bed rest is required to arrest certain types of cases and what can be expected from rest and from the various forms of major and minor collapse. They have developed formulas for the management of different types of cases. These formulas have now been completely upset by the introduction on one side of the equation of an unknown factor. They knew for instance that in minimal tuberculosis the formula was

Bed rest (6 months) plus partial rest (6 months) — cure. Now with streptomycin added the formula is

Bed rest (? months) plus partial rest (? months) = cure. It will require many years and long clinical experimentation to answer these questions. But at the present time one *is safe in assuming that streptomycin has not* changed the treatment of tuberculosis. It has merely strengthened a treatment which has always been inadequate and uncertain. One should continue to use the old formulas and to consider streptomycin an adjunct *which will make success more common.*

Thus far one can conclude

(1) Streptomycin is almost a specific remedy for miliary tuberculosis and for intestinal laryngeal and vesical tuberculosis

(2) In acute and chronic tuberculosis it has an important favorable effect obviating the necessity for collapse in milder cases and bringing many far advanced cases back into the group in which collapse can be used

(3) It greatly reduces the incidence of hemorrhage and sudden spread of the disease to new lung areas and also of the extra pulmonary complications of tuberculosis

(4) It renders spreads during surgery and general anesthesia much less common

(5) All in all it has greatly reduced the death rate from tuberculosis

(6) Used with care and in proper dosage it has no serious complications. What complications it has are less important than the dangers of serious tuberculosis and can be avoided in cases which might recover without it

(7) It should therefore be used in all cases

The Types of Pulmonary Tuberculosis and Their Treatment. Pulmonary tuberculosis is not a single disease. The tubercle bacilli reach the lungs by various routes and the forms of disease caused by each type of pathogenesis differ profoundly. The basic distinction is between the hematogenous and the bronchogenous routes of infection. Within the hematogenous group the route is probably always the same the disease

the resistance of the individual and the virulence of the organisms. Clinically the disease varies from acute miliary tuberculosis to the most chronic and smoldering types of phthisis. It may be classified as follows

(1) Acute progressive miliary tuberculosis
(2) Cold miliary tuberculosis, the French *tuberculose miliaire froid*
(3) Chronic hematogenous tuberculosis
  (a) early subacute stage
  (b) middle chronic stage
  (c) late chronic stage

Miliary Tuberculosis. The clinical picture and course of acute miliary tuberculosis are well known. The source of the infection is an active tuberculous lesion either in the thoracic duct or some blood vessel which continuously feeds large numbers of bacilli into the blood stream. This may involve many organs or chiefly the lungs or one lung or only the meninges or the liver. The disease is practically always steadily progressive and fatal, the infection extending past its original site to involve many organs and eventually the meninges.

Before the discovery of streptomycin there was no effective treatment. Streptomycin will cure most cases if it is used before the meninges become involved. The dosage should be large and the course prolonged. It should be combined with a long period (6 months to one year) of complete bed rest [illegible] after the

made to make an early diagnosis and to start treatment at the inception of the disease

Cold miliary tuberculosis has the same

pathogenesis and the same roentgenologic picture as acute progressive miliary tuberculosis Just why the symptomatology and course are so different is uncertain There is little or no fever slight cough and no dyspnea Response to simple rest in bed is often good the lesions in the lungs often clearing completely There is the same danger of meningitis and also of the development of localized infections in other organs The treatment is administration of streptomycin and rest as in progressive miliary tuberculosis

Chronic Hematogenous Tuberculosis Subacute and chronic hematogenous pulmonary tuberculosis is a distinct and important type of chronic phthisis differing profoundly from the bronchiogenic type in its symptoms its course and in the indications for treatment It is poorly understood even by many phthisiologists is often con

focus in a lymph node adjacent to a blood vessel which sends occasional showers of bacilli into the blood stream

It is an extremely slow creeping infection which progresses insidiously over many years producing few or no symptoms either local or general until it is far advanced In all save its late stages the pulmonary and systemic symptoms and signs are so slight that when by chance it is found on the roentgenogram it is often considered to be a healed lesion For the same reasons the first important symptoms are often those of some extrapulmonary complication such as laryngitis enteritis fistula in ano or some focus of skeletal tuberculosis Cases are thus often referred to the phthisiologist by the laryngologist the urologist the proctologist or the orthopedic surgeon

It is usually symmetrically bilateral and apical although it may occasionally be unilateral or even basal In its early stages it shows on the roentgenogram as coarse miliary seedings usually in both apices Over the course of years it extends gradually downward until all or both lungs may be involved The older denser and more fibrotic lesions are in the apices Eventually excavation occurs The cavities are thin walled and therefore difficult to distinguish They are usually in the upper lung areas and in both lungs

The involvement develops over many years so that the disease becomes clinical only in the third fourth or fifth decade of life Except in the late stages cough is slight and expectoration scanty Bacilli are usually hard to find and are often discoverable only by guinea pig inoculation Extrapulmonary complications are common Occasionally the

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early stages treatment scarcely seems indicated and in all save the extremely late stages response to treatment is extremely rapid and misleadingly satisfactory After a few weeks or months in bed rapid gain in weight and the disappearance of all signs and symptoms even of bacilli from the sputum convince the patient and too often the physician that arrest has been accomplished For these reasons most cases are undertreated They return to work and then back to the sanatorium again and again each time with more advanced disease until finally they no longer respond to treatment and are no longer curable

This type of tuberculosis requires prolonged rest in bed and often either unilateral or bilateral collapse Streptomycin should

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far advanced and chronic cases Experience with streptomycin and pneumothorax indicates that safe healing has been accomplished only when the lesions have either disappeared or are well collapsed

In the bilateral cases and most cases are bilateral a course of streptomycin and 6 to 8 months of rest in bed will usually clear all save the older and more fibrotic lesions in the apices At this point collapse must be considered It can safely be omitted only if nearly all of the lesions have resolved and all cavities have closed Small residual cavities are particularly difficult to recognize by any means save planography If cavities persist collapse must be used. Artificial pneumothorax or extrapleural pneumonolysis are the procedures of choice Because the disease is usually bilateral thoracoplasty is rarely indicated and bilateral intrapleural or

extrapleural pneumothorax are often demanded Phrenic nerve block on the worse side, alone or with pneumoperitoneum, may be used early

Bronchogenic Tuberculosis Bronchiogenic tuberculosis differs from chronic hematogenous tuberculosis in almost every characteristic Whereas the latter is usually smoldering and steadily and slowly progressive, the bronchiogenic form is often flaming and febrile, progressing early to caseation and excavation and traveling from lobe to lobe and lung to lung by a series of relatively closely spaced acute incidents Hematogenous tuberculosis is usually bilateral, but the bronchiogenic type in its early stages is nearly always unilateral, becoming bilateral not by its nature but as the result of an accidental spill of bacilli into the unaffected lung While hematogenous tuberculosis is primarily a disease of the middle decades of life, the bronchiogenic type affects chiefly young adults and occasionally older people whose resistance has diminished With this form, extrapulmonary complications are rare, with hematogenous tuberculosis they are common

Within its own category, bronchiogenic tuberculosis varies tremendously, the variations depending on the pathogenesis, the number of bacilli which establish the infection, the stage of the disease and also the variable relationship between the allergy and resistance of the individual and the virulence of the organism It is a striking fact that in any individual recurrences or spreads of the disease follow a pattern peculiar to that person The picture of the disease varies from the symptomless early infiltrate or the purely bronchial irritation of a perforating lymph node, through acute bronchopneumonia or lobar pneumonia on through all stages of extent and chronicity, from progressive and rapidly fatal widespread caseation to a chronic, almost asymptomatic, fibroid tuberculosis

The pathogenesis of reinfection bronchiogenic tuberculosis is either exogenous or endogenous, i e, the bacilli either reach the lung directly by inhalation from some source outside the body or are disseminated in the air passages from some part of the primary complex, either from the focus in the lung or from a hilar lymph node In exogenous reinfection the mechanism is single and obvious, in endogenous reinfection it is various

The Progressive Primary Infection Now that the primary infection is so often postponed past the highly resistant period of childhood and into puberty and adulthood

into phthisis This may occur as the result of excavation and extension of the lung focus but more frequently from rupture of the enlarged hilar lymph nodes into the lung or into a lobar bronchus The marked involvement of these glands is the chief characteristic of primary tuberculosis and is what makes the progressive primary infection different clinically from late reinfections The enlarged nodes often press upon the bronchus narrowing it and producing a wheeze and later an atelectasis Cough wheeze, and perforation with positive sputum may occur before there is any obvious parenchymal involvement or the first evidence of the disease may be a massive tuberculous pneumonia from sudden rupture of a caseous and purulent gland into the bronchus The spilling of bacilli may, however, be slight, producing only a little bronchopneumonia or even only one or more infiltrates

It is important to recognize this type of lesion, as it is the one most often leading to severe bronchial tuberculosis and to stenosis The explosive cough often threatens spread to other lung areas Use of streptomycin is imperative and early collapse or even excision may be indicated Light doses of roentgen rays over the hilar region may [illegible] f the nfect on in the [illegible] y case [illegible] n this manner and that active treatment in the [illegible] nce [illegible] llo [illegible] on [illegible] mary tuberculosis [illegible] des reflect the parenchyma must be reversed to [illegible] the par [illegible] mary infection tubercle bacilli remain alive

in the elements of the complex Late reacti vation of the primary pulmonary focus is rare but reinfection from reactivated hilar lymph nodes is common These too may cause severe bronchial tuberculosis and bronchial stenosis and atelectasis

onset and course of the disease depend on the dosage of bacilli and the reaction of the individual The sudden rupture of a caseous lung or gland focus produces an extensive bronchopneumonia or lobar pneumonia while the aspiration of a few bacilli as in exogenous reinfection produces a tiny area of bronchopneumonia with few or no symp toms and soon rounds up into an "early infiltrate" The severity of the reaction the amount of perifocal exudate and the tend ency to caseation excavation and progres sion all depend on the allergy and resistance of the particular patient and probably also on the virulence of the offending organ isms In some resolution and clearing occur without caseation and excavation and in others these processes are rapid and exten sive In each case every recurrence and spread tend to follow the pattern of the original lesion

Progress and extension of bronchogenic tuberculosis are rarely steadily progressive They occur usually by a series of acute inci dents as bacilli are aspirated into new pul monary areas These extensions may be

treatment More often it becomes caseous and breaks into the air passages leaving a cavity at its site and producing a contiguous area of bronchopneumonia From this point on when the sputum has become frankly positive and excavation has occurred all cases of bronchogenic tuberculosis are roughly similar Progression from lobe to lobe and lung to lung by aspiration of bacilli is the rule

We have then the following types of pulmonary tuberculosis

(1) Hematogenous tuberculosis
   (a) acute miliary
   (b) subacute miliary
   (c) chronic hematogenous
(2) Bronchiogenic tuberculosis
   (a) the primary complex
   (b) the progressive primary complex
   (c) late autogenous reinfection
   (d) exogenous reinfection

Reinfection The Treatment of Types of Bronchogenous Tuberculosis THE EARLY INFILTRATE The early infiltrate a round sharply delimited focus is the earliest demonstrable form of bronchogenous tuber culosis It is the result of a small area of bronchopneumonia caused by the aspiration either from an exogenous or an endogenous source of a small number of tubercle bacilli. It may cause fatigue or even hemoptysis but is usually asymptomatic It is of tremendous importance because it is the breeding ground for large numbers of bacilli which may es cape either gradually or suddenly to infect other lung areas and produce widespread clinical tuberculosis It may heal without treatment but usually in young adults and too frequently in all age groups the center of the infiltrate caseates liquefies and fi nally breaks through to discharge large num bers of bacilli into the surrounding lung The larger it is the more likely is it to do this and the less likely is it to heal by con servative treatment (see tuberculoma)

Such a lesion found on a routine roentgen ogram poses an important diagnostic prob lem It must be distinguished from the pul monary focus of primary tuberculosis from coccidioidomycosis from a benign or ma lignant tumor and from an old healed lesion In every instance the physician must decide whether it is tuberculosis and if so whether it is active and dangerous or old and safe

Since some infiltrates will heal with no treatment no one can tell how little treat ment is needed in any given case He must aim therefore to give that amount of treat ment which will produce a cure in practically 100 per cent of cases

Before the advent of streptomycin one could feel safe in prescribing 6 months of bed rest and 6 months of graduated exer cise If streptomycin is used these periods can probably be shortened but at the pres ent time no one knows to what extent One would be justified in trying a series of cases on 3 months of bed rest and 3 months of limited activity

Many phthisiologists feel that streptomycin

should not be used in minimal tuberculosis They maintain that it is not *needed and that* it is unwise to render the bacilli resistant and so decrease the effectiveness of the drug *should* the *infection* recur or spread This danger is more imaginary than real If the cases are properly handled 90 to 100 per cent should remain well and should the disease recur larger doses of streptomycin could be used and other more radical methods of treatment

Some clinicians use *phrenic nerve block combined with shortened periods* of bed rest and inactivity

Artificial pneumothorax is a good safe and sure method of treatment It is indicated when there is need for an early return to work or where the normal life of the individual *is certain to be strenuous It should* be preceded by a few months of bed rest

TUBERCULOMA *Infiltrates vary in size and* their tendency to central liquefaction and evacuation is greater in the larger lesions These larger infiltrates are called tuberculomas Some of them do heal completely and remain in the lung as annular opacities which are with difficulty distinguished from benign or malignant tumors Those that do not heal persist as thick walled cavities which because of the thickness of their walls rarely close spontaneously and are difficult to *close by collapse measures They may* appear to close and heal but often this means only that they have become filled with inspissated secretions which will again liquefy and be evacuated

Active or recurringly active tuberculomas are often an indication for lobectomy or partial lobectomy This does not mean that all large infiltrates should be immediately excised In tuberculosis there is no rule or indication that is universal Many of them *do heal on simple bed rest and streptomycin* or on pneumothorax These measures should be tried first and resection reserved for those that do not respond or appear *unlikely to* respond to the simpler treatment

THE EARLY INFRACLAVICULAR CAVITY WITH BRONCHOPNEUMONIA This is the classical picture of early bronchogenous tuberculosis Although the early infiltrate may occur any place in the lung from the extreme apex to the base it is most common in the posterior *portion* of the upper lobe at a level which on the usual roentgenogram places it in the *infraclavicular region* When an infiltrate evacuates it most often does so quite suddenly spilling secretions rich in tubercle bacilli into the surrounding lung area and producing quickly a cavity surrounded with a greater or lesser amount of bronchopneumonia

When such a lesion first develops it is *what is called "hot" This means that there* is still an active and acute tissue reaction *and that about each focus of tuberculosis* there is an area of perifocal exudate Any active interference at this stage is apt to do more harm than good Artificial pneumothorax is almost invariably followed by an acute pleurisy and the collapsed pneumonic areas often undergo organization and fibrosis rather than resolution The patient should be put on absolute bed rest and streptomy

Before the advent of streptomycin such contralateral spread was common even while the patient was under treatment and

sease

these

aring

of the exudate and decrease in the size of the cavity are almost the rule After a preliminary *period of bed rest and streptomycin* phrenic nerve block or this and pneumoperitoneum may reasonably be employed One hopes that the lesion will clear and *the cavity close* without further interference Cavity closure is the great question and the great problem and the use of these essentially benign procedures during the period when the lesion is most labile certainly favors the closure of the cavity and so may do much to obviate the necessity for subsequent major surgery

If pneumothorax is to be used either as a procedure necessary for the closure of cavities or as one of choice to hasten and *make certain of recovery* it had best be postponed until nearly maximal benefit has been obtained from bed rest. The smaller the cavity and *the more quiescent the disease* the more likely is pneumothorax to be successful and uncomplicated

Major surgery thoracoplasty *should* be resorted to only when all other measures have proved unsuccessful

In this type of unilateral or predominantly unilateral disease there is a tendency to overlook or ignore small lesions in the opposite lung An infiltrate or a small area of involvement seems little in comparison to the predominant lesion If a little focus in the opposite lung were all of the disease, one would take it seriously and treat it by prolonged rest or pneumothorax Actually one has a tendency to forget it and where collapse is used early on the worse side to permit too early activity Many of the reactivations following successful pneumothorax develop from small lesions in the opposite lung which have been neglected When one treats tuberculosis on the basis that it is unilateral he must be sure that it is truly unilateral

Large Apical Cavities Extremely large cavities in the apex of the lung are not readily closed by pneumothorax or even by thoracoplasty Many of these are tension balloon cavities in which air is entrapped under pressure This prevents collapse Others are simply too large to have their walls approximated by the amount of collapse which a thoracoplasty can provide

Many of these will so decrease in size on bed rest and streptomycin that thoracoplasty can eventually be used

If they remain large they can be handled in one of two ways either by excision or by Monaldi's suction followed by thoracoplasty

Cavities in the Apex of the Lower Lobe Most cavities which appear close to the hilus are in reality posterior to the hilus in the apex of the lower lobe Bed rest streptomycin and phrenic nerve block are almost specific for cavities in this location In most instances they close rapidly and completely Pneumoperitoneum may also be used

If such a cavity persists in spite of conservative treatment pneumothorax should be tried If this is unsuccessful excision is the procedure of choice Thoracoplasty is rarely effective

Cavities in the Lower Portions of the Lower Lobe In contrast to cavities in the apex of the lower lobe which are easy to close those in the base are extremely resistant Phrenic nerve block and pneumoperitoneum which theoretically should be most effective usually merely raise them higher in the chest If these will not close with pneumothorax lobectomy is indicated

Bilateral Bronchiogenic Tuberculosis *In bronchiogenic tuberculosis the disease has always started in one lobe of one lung and has spread from there into other lobes and into the opposite lung by a series of spills* For this reason one lung usually is more extensively involved than the other and the lesions in the opposite lung may vary from minimal infiltrations to far advanced disease with cavitation

Minimal and moderately advanced disease in the opposite lung will heal on bed rest and streptomycin so that the lung more seriously affected may eventually be handled as if the disease were truly unilateral If however the disease is more extensive the problem is much more difficult One must then take full advantage of every form of treatment

Nearly every such case should be kept on bed rest and streptomycin and perhaps pneumoperitoneum until maximal benefit has been obtained from these procedures Direct collapse should be started only when progress has stopped (4 to 8 months) or when hemorrhage or severe cough threatens spread of the disease or extension does actually take place One must aim always to arrest the disease in the lung less seriously involved so that surgical collapse may be used on the opposite side Bilateral pneumothorax may be successful but often it is necessary to use pneumothorax on the better lung as a preparation for thoracoplasty on the opposite one If this is successful it is the easiest way out *If it is impossible, one* may have to use one of many combinations of bilateral surgical treatment i e bilateral paraffin packs or pack on one side and thoracoplasty on the other or thoracoplasty or pack on one side and Monaldi's suction or cavernostomy on the other In such cases *one must choose from his armamentarium* and mix and combine the procedures to meet the particular situation in each lung area

Bronchial Tuberculosis Tuberculosis of the bronchi is relatively common and is one of the most important of the complications of pulmonary tuberculosis It may develop either as the result of *implantation of the* mucous membrane or by direct extension from the hilar lymph nodes These may com

press erode or perforate the bronchus during the primary infection or much later latent and apparently healed infection in them may become exacerbated and do the same things

Involvement of a bronchus becomes important only when it causes bronchial narrowing When this occurs the lobe or lung does not drain well and the tuberculosis in it tends to remain active Cough is often or usually severe and explosive and the narrowed bronchus acts as an atomizer through which infected secretions are sprayed widely to other lung areas If the bronchus becomes extremely narrow plugs of mucus frequently block it completely causing a retention of secretions and an elevation of temperature When the plug is finally coughed out production of sputum recommences and the temperature falls If the bronchus becomes completely stenosed by scar tissue the lung distal to it may heal in complete atelectasis This is a rare termination and is not to be expected

Small implantation ulcers in the bronchus are common and not of great significance They usually heal as the pulmonary lesions heal or are collapsed It seems probable that most important bronchial tuberculosis develops by extension from peribronchial lymph nodes and that in these instances the bronchial perforation is the cause of the pulmonary infection This is suggested by the clinical observation that most cases of serious bronchial obstruction commence with the symptom of wheezing and that the picture of bronchial stenosis is present from the onset It is further suggested by the fact that one occasionally sees cases of bronchial tuberculosis which have not yet developed parenchymal lesions If these are watched pulmonary tuberculosis eventually develops and often with the sudden onset of atelectasis

This mechanism is common in primary tuberculosis in which glandular involvement predominates It can also develop late from exacerbations in quiescent glands In these days when the primary infection is so often delayed until an age when resistance to tuberculosis has fallen off it seems probable that many of the cases of severe bronchial tuberculosis are the result of such a progression from a first infection

The immediate threat from bronchial tuberculosis is in proportion to the severity of the cough In some acute cases this is so extreme that wide dissemination from what at first seems a small and relatively unimportant lesion is rapid

The treatment of bronchial tuberculosis with stenosis is usually excision Cases vary so greatly and respond so variously to other forms of treatment that no hard and fast rule can be laid down There is a tendency to be conservative and usually conservatism is poorly rewarded By observing the nature of the lesion the severity of the cough and the amount of sputum one can tell in which cases delay and the trial of other methods are safe The great danger is spread to the opposite lung

The early hope that streptomycin would be as effective in this type of tuberculosis as in that of the larynx has not been fulfilled It will usually cure small implantation ulcers but is only temporarily successful in the severe forms

When the narrowing is caused by the acutely enlarged glands of a progressive primary lesion streptomycin and the natural course of the disease in which these subside and contract will frequently result in reopening of the bronchus and clearing of the tuberculosis

Cauterization of the ulcers with 10 per cent silver nitrate solution is sometimes effective and should always be tried

Pneumothorax is usually effective temporarily and sometimes permanently By cutting down the cough it lessens the danger of spread and by decreasing the flow of bacilli over the affected bronchus it favors healing The immediate good results are often misleading and it should be used and persisted in only in cases in which there are definite contraindications to thoracoplasty and excision

Thoracoplasty may well be tried before excision It will frequently produce a satisfactory result but if wheeze positive sputum or "damming spells continue lobectomy or
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as a complication of obvious parenchymal lesions or may occur as an apparently independent disease In the latter case one must

assume that the lung is minimally involved In both cases treatment must be directed chiefly toward cure or prevention of the pulmonary tuberculosis

In nearly every instance the pleurisy itself is a relatively benign self limited disease The fever subsides and the fluid resorbs over a period of several weeks If the outpouring of fluid is so excessive as to produce dyspnea

pleura will become so thickened (even calcified) that the lung will be prevented from re expanding In most cases aspiration is neither necessary nor advisable

Some phthisiologists have advised converting the pleurisy into a pneumothorax and continuing the collapse for a year or two in order to prevent development of tuberculosis in the lung This means that the pneumothorax at its initiation is complicated by an acute pleurisy and therefore that the pleura will become thickened and re expansion difficult. The procedure seems indicated only if there are lesions in the lung which appear definitely to need collapse

The great danger of idiopathic tuberculous pleurisy with effusion is the subsequent development of pulmonary tuberculosis This may occur a few months or many years after the acute disease and in spite of the fact that at the time of the pleurisy the lung appears free of disease It is estimated that between 35 and 45 per cent of cases later develop consumption unless they are treated for consumption at the time of the pleurisy

Every patient should be treated as if he already had a minimal pulmonary tuberculosis This means that he should have approximately 6 months of bed rest in a sanatorium and a further 6 months period of *partial rest at home Following this* he should be checked by periodic roentgen ray examinations for the remainder of his life

Streptomycin in small doses may be used during the acute stage of the disease

The Patient in the Treatment of Pulmonary Tuberculosis We have spoken thus far of the methods of treatment and the types of tuberculosis It remains to say something concerning the patient as a human being who has psychologic social and economic problems peculiar to himself To an important

ologist must be to make tuberculosis an incident in the normal life of the patient rather than an altering and revolutionizing disaster He should assume that his function is to return the patient as soon as possible to his home and to his former career and occupation or at least to a career and occupation which are normal for an individual of his age and abilities The old idea should be abandoned that a bout with tuberculosis forbids forever hard work marriage childbearing or any normal activity as should the new idea that it should be made the occasion for months and years of re-education and rehabilitation The phthisiologist should consider himself as a curer of a disease rather than as a re educator or a meddler in the normal lives of his patients

One can say definitely that that person recovers best who recovers with the least mechanical interference or with that which is the least drastic and the least subject to complications But one knows also that collapse of a lung by pneumothorax or even thoracoplasty will greatly hasten recovery will greatly lessen the chances of recurrence and will permit a more strenuous life On this basis one will treat one case of minimal tuberculosis with 6 months in bed and 6 months of restricted life another with 3 months in bed and pneumothorax still another with immediate pneumothorax and return to work after a few weeks Young people who are naturally energetic and active and who must and should be so if they are to establish a position in life probably should all have pneumothorax This is particularly true of medical students interns and residents mothers with small children or young women who should have children in the near future

In all of this one must steer a middle course governing his procedure by what he thinks is the patient s need and not being influenced by the patient s preference He will be under constant strong pressure to cut corners to omit sanatorium care to shorten bed rest to proceed early to collapse to delay collapse too long etc etc He must resist all of this and firmly and yet at the

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same time must make all reasonable and safe allowances for the patient's peculiar necessity

The physician's first task is that of a persuader or convincer The treatment for tuberculosis is bitter to take and this bitterness is usually out of all proportion to the symptoms and the sense of illness When a well or relatively well person is told that he has tuberculosis and must leave his home and work and go to a sanatorium often his first *reaction is to refuse to believe the diagnosis* and then to say that he cannot or will not follow the advice The mother cannot leave her home and children or the husband his job This reaction is natural is a transient hysteria which should not be taken *seriously* and is almost the rule It is moreover a crucial period in the treatment If the physician fails here he has failed completely and an hour or two spent in convincing the patient of the necessity and feasibility of the treatment is better used than an equal amount of time spent later in performing a *thoracoplasty Throughout the course of* treatment tact understanding and persuasion in holding the patient to the difficult regimen are constantly required If the *patient does not accept treatment or abandons* it before it is completed this is the doctor's fault and not the patient's He cannot say "take it or leave it" He must persuade the *patient to take it and any sanatorium physician* who has a large number of patients who insist on leaving against medical advice is not a good physician regardless of his knowledge of indications or his skill in technics

The time element in the treatment of tuberculosis is basically important A person *may step out of the ranks of society for* 6 months or a year or even for 18 months without being left too far behind and without losing the will or the ability to take up and go on This is not so if he is out for 2 or 3 or 4 years Then his position in business or even in the home will have been filled and he himself will have become too adjusted to the *ways of the invalid*

Furthermore the time which each individual may reasonably spend varies tremendously as does the type and *strenuousness* of the life which he must resume Some personalities and some age groups can be trusted to take good care of themselves and others cannot

Treatment must be chosen and applied *with reference to all of these demands* and variations and in every instance the patient must be allowed to take a calculated risk never too great but always in proportion to the requirements of his situation In advanced and desperate cases *all of this must* be forgotten In these the patient's very life is at stake and every other consideration is unimportant But in the great majority of cases the question is not "Will the patient recover?" but "How and when will he recover?" and in these cases the treatment must be cut to fit the situation

The duration of invalidism is determined by the time required to obtain maximum benefit from rest In all save exceptional cases bed rest in a sanatorium should be the first phase of treatment It should be in a sanatorium because only there can the patient be held to the strict regimen and only there can he be adequately educated in the *nature of the disease which he must com*bat Rest and streptomycin and perhaps [illegible]

hot is likely to lead to co[illegible] because all clearing of exudate and all de-[illegible] rest

simply for its own sake because every case should have it *The tuberculosis which one* sees on the roentgenogram is never all that is present Often there is important disease in the hilar lymph nodes and nearly always [illegible] Only by

[illegible] are being given a chance to heal

All bilateral cases unless extension is actual or is too greatly threatened should be continued on rest as long as improvement continues in the hope that one or *even both* lungs will heal completely so that bilateral collapse can be avoided

One should not assume that in every case rest and streptomycin will stop progression *All cases must be watched carefully* especially those with acute exudative disease Every patient should have a roentgen ex

amination each month and the acute cases each week or two The course of each case as shown by these roentgenograms must determine whether rest will be continued or whether additional treatment has become necessary

The improvement obtained from streptomycin and complete bed rest decreases steadily and in something between 6 and 8 months stops completely It is greatest the first month, less the second less the third, and so on until finally there is no further change The time required for this curve to flatten into a straight line determines largely the time required for the arrest of all curable cases During the first 8 months some lesions will have cleared completely and others in which collapse is to be used as a procedure of choice will already have had it These cases will be ready for discharge to continue partial rest and graduated exercise at home Those which have not cleared will have secured maximal benefit from bed rest and must now be considered for collapse or excision or whatever interference seems indicated

It must be remembered that tuberculosis is a general and not a strictly local disease and that, therefore, every case benefits from a period of bed rest, it must be remembered that the complications of collapse are in proportion to the extent and the acuteness of the disease and that its effectiveness is in proportion to the quiescence of the lesions and the size of the cavities For these reasons the early use of collapse does not hasten and assure recovery and does not shorten the

ities and the conversion of the sputum, has been established

But to return to the time element in the treatment of tuberculosis One should assume that every curable case, even the most advanced, will be arrested and ready to return to work in 18 months This limit is determined by the time required to obtain maximal benefit from complete bed rest—4 to 8 months—and the time required for the application of and the recuperation from collapse therapy Many milder cases can return to work much sooner, but even the most advanced should be well in a year and a half

Graduated Exercise and Rehabilitation. The formalization of graduated exercise and rehabilitation in the sanatorium, a practice which is being emphasized at the present time, should be avoided It is in line with the current tendency in social thinking in which the individual is considered as a poor homeless jellyfish who has no sense or personal responsibility and who must be continually guarded and guided by the professional psychologist and the trained social worker Because of this conception, sanatoria are cluttered with people walking by prescription and being so intensively rehabilitated that they never rehabilitate themselves

The sanatorium should be considered as a place for the enforcement of strict and complete bed rest and for the initiation of collapse measures If the patient has a home that is at all livable and most persons do, graduated exercise should be taken at home and rehabilitation should be returning to work He should do all of this under the care and guidance of the physician who has cared for him in the sanatorium As early as possible he should be put back into his normal milieu and should be treated as a self-responsible, self reliant individual, and not as a special case who asks or needs prolonged protection and continued aid

Hemorrhage in Tuberculosis Hemorrhage in pulmonary tuberculosis is either rapidly fatal or automatically self-limited If the bleeding vessel is so large that the flow of blood is more than the patient can evacuate by expectoration, he drowns in his own blood in the course of a few minutes Fortunately, such profuse hemorrhage is rare In the majority of instances the vessel involved is so small that evacuation of the blood is easy and clotting within the vessel occurs in a few minutes Hemorrhages of this kind are serious only because of the great chance that aspiration of bacillus-laden blood into uninvolved lung areas will result in wide dissemination of the disease It is important, therefore, that the bleeding be stopped and that retention of blood in the air passages be prevented

The bleeding may be stopped by absolute body rest, by the parenteral administration of substances favoring coagulation, or by collapse of the involved lung area Streptomycin

is of the utmost importance in the prevention and treatment of hemorrhage and also in preventing spread of the disease to new lung areas The spilling and retention of blood can be prevented by withholding cough reducing narcotics and informing the patient of the extreme importance of ridding himself of the blood by easy throat clearing efforts as fast as it accumulates Patients tend to suppress cough for fear of stimulating the bleeding and when this tendency is encouraged *by the administration* of large doses of morphine or codeine *retention of* blood and dissemination of the disease are almost certain

The patient should be put on absolute bed rest with an ice bag on the affected side of the *chest* Vitamin K *and thromboplastin*

is copious or continued or if it tends to recur *in spite of conservative measures the lung* should be collapsed Collapse by artificial pneumothorax will stop most bleeding almost immediately

Diabetes and Tuberculosis Diabetes predisposes *to infections of all varieties among* them tuberculosis Tuberculosis in the diabetic is more difficult to control than in the nondiabetic and diabetes is more difficult to control in the tuberculous than in the non*tuberculous This greater tendency of tu*berculosis to develop and spread in the diabetic is caused by the high blood sugar The basic problem of the treatment of tuberculosis in the diabetic is therefore the *maintenance of a normal blood sugar Once* this has been accomplished and as long as it is maintained the treatment is no different and no more difficult than in the nondiabetic One must however assume that the blood sugar will *not always be kept normal* and for this reason must treat the diabetic longer more rigorously and more radically than the nondiabetic Recovery without collapse should rarely be counted on Pneumothorax *should be used as a procedure* of choice even for minimal lesions and once established should be maintained longer than is usual The permanent collapse of major surgery ... resorted to and small ... aken ... car... ried out if every effort is made to keep the blood sugar normal and if the treatment is more intense and radical *the results* will be as good and permanent as in the nondiabetic.

Pregnancy and Tuberculosis The resistance to the development and spread of tuberculosis is greatly reduced during the *postpartum period At this time the disease* is peculiarly apt to develop or if already present to be aggravated For many years young women who had had tuberculosis were advised never to marry or have chil*dren and abortion was regularly prescribed* for pregnancy in the tuberculous

With the present methods of treatment these drastic restrictions against childbearing and this indication for abortion save in exceptional circumstances are no longer necessary Marriage and the bearing of children are important parts of a woman's life and to forbid pregnancy or to terminate it is a serious matter If the treatment of the disease *is* carried out with due *allowance for this* added risk the danger can be largely eliminated As in diabetes pneumothorax and surgical collapse should be more freely resorted to and pneumothorax should be main*tained for a longer period in most instances* until 2 or 3 children have been born Particular precautions should be observed during each postpartum period and as far as possible during the whole period All in all *the situation should be handled in* accordance with the modern concept of tuberculosis as an incident in the normal life of the patient rather than as a cause for chronic invalidism

Jerome R Head

GENITO URINARY TUBERCULOSIS

Genito urinary tuberculosis is usually secondary to tuberculosis elsewhere in the body Not infrequently the original lesion may be absent or obscure Unlike tuberculosis of the lungs it *is impossible to put the urinary* tract at rest However all other measures such as good food sunshine and mental and physical rest are helpful in the treatment.

In the past many urologists thought that tuberculosis *of the urinary* tract attacked only one kidney the other kidney being free of the disease A more modern concept now prevails namely that tubercle bacilli pres

ent in the urine never occur unless a local lesion is present Tuberculosis of the kidney may heal and disappear and as a rule the infection is bilateral at its onset At one time much was made of "autonephrectomy By autonephrectomy the pathologist described a tuberculosis of the kidney with an obstructed ureter the patient making what appeared to be a recovery from his infection This occurs rarely and is not to be hoped for in the ordinary case of tuberculosis

Medlar found at necropsy that where the urinary tract was infected in tuberculosis the so called healthy or uninfected kidney revealed healed tuberculous lesions

For many years the treatment of urinary tuberculosis was surgical In those cases of bilateral renal tuberculosis or where the patient refused surgery the prognosis was indeed grave Even in unilateral tuberculosis where nephrectomy is done Wildbolz Emmett and Gile found that the 5 year cures reported from various groups rarely exceeded 50 per cent

In the past 2 years streptomycin has been used in the treatment of tuberculosis and sufficient time has not elapsed to evaluate accurately its effect The experience with streptomycin has been sufficient however to show that it stimulates healing in many *tuberculous lesions and such complications* as poor wound healing fistulous tracts and tuberculous cystitis There are some reports in the literature by Nesbit where pus and the tubercle bacilli have disappeared from the urine and the patient appears cured There is no doubt that we may have to alter our method of treatment as our knowledge of the present and future antibiotics increases

Tuberculous Bacilluria without Symptoms Urologists are generally agreed that the kidneys in such cases have organic lesions present The patient despite the lack of symptoms should be placed in a sana

serves not only to eradicate the bacilluria but may prevent the development of clinical renal tuberculosis

Unilateral Renal Tuberculosis When a patient presents himself with definite clinical symptoms and signs of organic tuberculosis localized to one kidney judgment must be exercised in individualizing the treatment If the lesion by pyelogram appears to be a small erosion of a papilla or a fibrotic lesion the use of from 1 5 to 2 gm of streptomycin daily for 3 months is recommended A reexamination should be done to evaluate the status of the disease if improvement or cure has been effected the antibiotic therapy should be continued with careful observation In the event the disease does not improve or follows a downward course nephrectomy is indicated Where advanced unilateral renal tuberculosis has progressed to the caseocavernous type with extensive destruction of the kidney it appears that nephrectomy following preliminary treatment with streptomycin is best

Bilateral Renal Tuberculosis In these cases the surgeon has been reluctant to advise surgery with much hope Occasionally the removal of the more seriously affected kidney has resulted in temporary improvement But usually the added burden on the remaining infected kidney has proved disastrous Certainly in these patients the use of streptomycin will be of help in prolonging life and comfort for the patient

Tuberculous Epididymitis This is seen as a secondary manifestation of tuberculosis *elsewhere in the body Frequently tuberculosis* of the urinary tract is discovered with the advent of tuberculous epididymitis A careful urologic study is indicated in all types of genital tuberculosis Here likewise preliminary treatment should be with streptomycin probably followed by epididymectomy when it appears indicated A more radical operation was recommended by Young excision of the epididymis vas deferens seminal vesicles and prostate The more radical operation is infrequently attempted

Tuberculous Prostatitis This is rarely found as a separate clinical entity It is not infrequently seen as a complication of urinary tuberculosis A few cases have been mistaken for carcinoma of the prostate gland and total prostatectomy has been done with poor results General hygiene rest avoidance of sexual activity and conservative measures seem advisable Streptomycin may be of value but thus far enough experience with this drug has not been reported Mas

sage of the gland and local treatment are contraindicated.

Tuberculous Cystitis. Good results have been reported with the use of streptomycin in cystitis following nephrectomy for tuberculosis. Formerly the cystitis associated with renal tuberculosis continued for months and years following nephrectomy. Various drugs

ent streptomycin gives rapid and dramatic relief in these patients with postoperative cystitis.

Tuberculosis of the Penis. This is a rare disease and in most patients appears to be a cutaneous type of disease. The treatment belongs in the hands of the dermatologist.

One must realize that the treatment of tuberculosis in general may be radically changed as a result of streptomycin. It would appear that our surgeons are beginning to *treat the patient as a person afflicted with a* general disease, rather than as a person with a localized lesion of the lung, kidney or bone. Undoubtedly surgery will be necessary in many cases where the local lesions are deleterious to health and resist medical treatment.

Recent reports in the literature by Youmans *and Pyle call attention to the development* or appearance of streptomycin resistant bacilli. Their work appears well founded *and the conclusions sound.* Whether or not this resistant strain of tubercle bacilli is more virulent or resistant to treatment remains to be determined.

In conclusion it should be emphasized that in all cases of tuberculosis *of the genito*-urinary tract co-operation between the attending physician and a competent urologist is important.

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FUNGOUS DISEASES

ACTINOMYCOSIS
(Lumpy Jaw, Streptothricosis, Nocardiosis)

Actinomycosis may be divided into the localized and well circumscribed type and the systemic type. The localized type usually has a favorable prognosis. The systemic type in the past usually resulted in death. The treatment usually relied on has been *iodine and its salts*, potassium and sodium iodide, copper sulfate, thymol, vaccines, roentgen rays, radium and surgery. With the onset of the era of the newer *chemotherapeutic* agents the prognosis of systemic actinomycosis has become much more favorable except in well advanced cases with extensive involvement of the brain tissue.

In spite of the newer chemotherapeutic agents the old mainstays still have a place in the treatment of actinomycosis but usually *in combination with sulfonamides* and penicillin. Each case is a problem in itself and *the type or combinations of treatment* must be judged accordingly.

The choice of treatment should depend upon the location, type, duration, extent and severity of the lesion. For the primary cutaneous type one form of therapy, usually the sulfonamides or penicillin, is sufficient. For the extensive cases and the systemic type a combination of several forms of treatment gives the best results.

Sulfonamides. In the primary cutaneous type one of *the sulfonamides preferably* sulfadiazine or penicillin is recommended. If sulfadiazine is the drug of choice it is ad

ministered as follows 2 gm at the beginning followed by 1 gm every 4 hours so that a satisfactory level in the blood is obtained This is continued until the lesion *shows evidence of clearing and is then reduced* so that a blood level of 5 to 10 mg per 100 cc is maintained A close watch for complications such as blood dyscrasia hematuria and skin eruption should be kept Exposure to the sun should be avoided while the sulfonamides are administered because of photosensitization

Penicillin If the organism is found to be sensitive to penicillin this antibiotic is preferable to the sulfonamides because of the less serious complications likely to accompany the administration of the drug Penicillin 50 000 units given intramuscularly every 3 hours around the clock is recommended Penicillin 300 000 units in yellow wax and peanut oil every 12 hours may be used in ambulatory cases If the patient proves to be sensitive to the vehicle crystalline penicillin which is water soluble may be employed in doses of 200 000 units three *times a day*

In systemic or extensive actinomycosis the ideal treatment is

(1) A high calorie and high vitamin intake to build up the natural resistance of the patient
(2) Ferrous sulfate 0 2 gm t i d if hypochromic anemia is present
(3) Bed rest

Penicillin 50 000 units intramuscularly every 3 hours may be given partly by the continuous intravenous drip method and partly by intramuscular injection as recommended by Hendrickson and Lehman In cases of central nervous system involvement well diluted penicillin can be given intrathecally *(50 000 units daily)*

A sulfonamide preferably sulfadiazine should be given starting with 2 gm and then 1 gm every 4 hours being continued until the patient appears to be clinically well and then for prophylactic reasons the sulfonamide should be continued in doses of 1 gm four times daily gradually reduced to 3 gm and 2 gm daily for a period of several months if any signs of relapse are noticed intensive therapy should again be resumed

Surgery should be postponed until after several doses of sulfonamides and penicillin have been administered except in cases in which immediate surgical intervention is necessary to relieve pressure and to alleviate pain Adequate surgical drainage is important All *sinus tracts should be exposed and* drained Necrotic tissue should be removed wherever possible In cases of intestinal actinomycosis resection of loops of intestine may be necessary Lobectomy and pneumonectomy are justified only when all other forms of treatment have been tried and failed

Roentgen therapy may be of value as a supplementary treatment especially in cases of indolent lesions Good results have been reported with fractional and intensive therapy with and without filtration

Iodides These may be given as a saturated solution of potassium iodide starting with 15 drops three times a day orally and increasing 3 drops daily to the point of tolerance Sodium iodide may be administered intravenously in 1 gm doses once a day in place of potassium iodide Tincture of iodine in milk o

times a (

point of

therapy Ethyl iodide inhalation therapy is of particular value in cases with bronchopulmonary involvement because it is the most direct route Ethyl iodide is nontoxic and highly volatile The coefficient of distribution between the alveolar air and the

demonstrated moreover that only a small proportion is returned in the venous blood so that the tissues are exposed to relatively large amounts of iodine The initial dose is 1 5 cc (3 gm) this is increased by 0 5 cc *(1 gm) per dose* until 3 cc (6 gm) is reached or in large patients 4 cc (8 gm) It usually requires about 30 minutes to inhale a dose of 3 cc of the mixture The necessary amount may be given in fractional doses during the day if the patient *is too* sick to inhale it all at one time To avoid cumulative effects inhalations are given on 2 successive days and then omitted on the third day It is advisable to use a mineral oil spray once a day to avoid irritation or an uncomfortable dry sensation in the throat A discussion of contraindications and pos-

sible complications is presented in the fol

sules (of 1 or 2 gm) once a day has been used as a supplementary treatment although the writer considers iodide in any form men tioned above preferable

Copper sulfate (¼ gr) given by mouth or colloidal copper administered intravenously has been used This form of therapy is not recommended

Local treatment by irrigation with peni cillin Lugol s solution or with 1 per cent gentian violet is of value

Vaccine Therapy This has been used with some success as a supplement to sur gery It may supplement sulfonamide or penicillin therapy or both if the patient fails to respond Colebrook recommends both stock and autogenous vaccine in doses of 5 000 000 to 10 000 000 mycelian fragments at intervals of 5 days

Streptomycin Streptomycin has not been used in a sufficient number of cases of ac tinomycosis for one to evaluate its thera peutic index in this particular disease Scattered reports have appeared in the litera ture Costigan reports the cure of a severe case of actinomycosis within 5 days after the institution of treatment with streptomy cin 250 000 units in 2 5 cc of sterile water every 3 hours The same patient did not respond to iodides penicillin and sulfona mides

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BLASTOMYCOSIS

In the treatment of North American blas tomycosis supportive measures such as a high vitamin and high calorie diet rest and sunshine are essential particularly in the systemic type Complete studies including roentgen ray and spinal fluid examinations should be done to determine whether dis semination to internal organs has taken place since the prognosis is much poorer particu larly when there is central nervous system involvement

Iodides Although iodide therapy is still the most effective weapon in this disease one must continue to search for more specific and effective therapeutic agents especially for systemic blastomycosis Iodide therapy was first used in cutaneous blastomycosis by Gilchrist Best results are obtained if the iodides are supplemented by roentgen ther apy and surgical procedures whenever *indi* cated The administration of iodide should be continued until all signs of active disease have disappeared

Martin and Smith advise desensitization with blastomycin in hypersensitive patients *before iodide therapy is instituted* They report an adverse effect resulting in the spread of the infectious process in hyper *sensitive cases* when iodides are adminis tered without at least partial desensitization for about 2 weeks They recommend the following technic A skin test with a stand ardized heat killed blastomycin vaccine is done by injection intracutaneously of 0 1 cc of the vaccine The size of the maximal reaction is determined by observation of the site of injection at intervals of 24 and 48 hours A reaction of 1 cm or more in diameter indicates hypersensitivity *The size* of reaction observed determines the dilution

of the vaccine required for the first desensitization A dilution of 1 100 is used for the first injection if the reaction is from 1 to 2 cm. in diameter A 1 1000 and 1 10 000 dilution is used for reactions of 2 cm and 3 cm in diameter respectively The proper dilution is injected subcutaneously beginning with 0 1 cc This dose is increased by 0 1 cc until 1 cc is reached Injections are given three times a week. This procedure is repeated with each lower dilution until undiluted vaccine is used A local or general reaction is a sign to stop injections These may be resumed several days later with a dilution ⅒th as strong as the one that produced the reaction Complete desensitization is not to be expected but a definite reduction in the size of the erythematous reaction takes place indicating a decrease in hypersensitivity

The most common type of iodide used is a saturated solution of potassium iodide in water or milk starting in the hypersensitive cases with as low a dose as 3 drops three

iod des as evidenced by a skin rash or running nose the drug should be stopped until all signs of iodism have disappeared and then resumed beginning with 3 drops three times a day and increasing by 1 drop daily until a dose of 20 drops three times a day is reached This dose should be continued until all active signs of the disease have disappeared In cases that do not show hypersensitivity to the intracutaneous injection of blastomycin a dose beginning with 15 drops three times a day and increased by 1 drop per dose to the point of tolerance is advisable

intravenously are advisable

Ethyl iodide inhalations are particularly useful in systemic blastomycosis with pulmonary involvement Potassium iodide may be given orally as supplemental therapy The dosage of ethyl iodide and the indications and contraindications are discussed in the section on moniliasis Ethyl iodide inhalations have been employed successfully by the writer and by others in the treatment of blastomycosis However failure to obtain permanently good therapeutic results in enough of the severe cases makes it necessary to search for a more specific therapeutic procedure

Copper sulfate in doses of ¼ to 1 grain (15 to 60 mg) administered orally three times daily has been reported effective The writer has had no experience with this form of therapy

Surgery Surgical removal of small and accessible foci is good treatment Large foci of infection may be drained Conant et al recommend deferring surgery until at least partial desensitization with blastomycin has been accomplished Surgical diathermy or actual cautery is not contraindicated

Roentgen Rays In cutaneous blastomycosis the use of filtered roentgen rays is advisable when surgical excision is not possible The dosage advised is 75 to 100 r filtered through 1 mm aluminum once a week It is not advisable to exceed a total dose of 1200 to 1500 r Conant et al warn against the use of roentgen therapy in patients with hypersensitivity to blastomycin before partial desensitization with injections of blastomycin vaccine has been produced

Vaccinotherapy Scattered reports of clinical improvement with vaccine injections have been presented Except for desensitization in cases with hypersensitivity as a supplemental treatment the value of specific vaccinotherapy is questionable

Antiblastomyces Rabbit Serum Martin reports the use of antiblastomyces rabbit serum with occasional benefit

Sulfonamides Several questionably favorable reports on the therapeutic effectiveness of the sulfonamides have appeared in the literature Most of the reported results coincide with our experience in revealing the sulfonamides to be ineffective Keeney demonstrated that sulfonamides are of no value in blastomycosis Noojin and Callaway found the concentrations required in vitro for inhibition of growth of *Blastomyces dermatitidis* to be well above the maximal clinical drug levels tolerated They therefore concluded that the sulfonamide compounds would be ineffective if used orally or parenterally in the treatment of blastomycosis

Streptomycin and Penicillin *Blastomyces dermatitidis* is rather resistant to both of these antibiot cs Their therapeutic value in this disease is doubtful

Streptothricin Because of its high toxicity, it is doubtful whether this drug will have clinical therapeutic value in blastomycosis, with the possible exception of its use as a

allantoic membrane of the developing chick embryo

Gliotoxin According to Meyer and Ordal gliotoxin showed a high fungistatic action in vitro on *Blastomyces dermatitidis* but was extremely toxic to the chick embryo

In *South American blastomycosis* iodide therapy has been reported effective in some cases by De Almeida The mode of administration is the same as that for North American blastomycosis Sulfonamides have been reported effective if given over a long period

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COCCIDIOIDOMYCOSIS

No specific drug is known for the treatment of this disease It is my belief and hope that a new antibiotic will be discovered that will prove specific

In a discussion of treatment it is more practical to discuss first the treatment of the primary pulmonary type and then the management of progressive coccidioidomycosis

Primary Pulmonary Coccidioidomycosis. *The object of treatment is to* afford the patient optimal conditions for localizing the infection Rest in bed is indicated until the temperature, white cell count, and sedimentation rate are normal, and the pulmonary

reliable index of the activity of the infection Symptomatic treatment, such as salicylates with or without codeine, may be administered Supportive treatment consisting of a high vitamin and high calorie intake during the convalescent stage is valuable Before the patient is discharged the physical signs

no specific treatment for progressive coccidioidomycosis The variety of drugs used in the past including the more recently tried sulfonamides and penicillin has not proved effective However, since there are some scattered reports of cures, present methods *of treatment should be considered*

Regardless of which type of therapy is tried, every effort should be made to support the general resistance of the patient by rest in bed and a high calorie and high vitamin intake

Since hypersensitivity to coccidioidin is a striking feature in the early stages of progressive coccidioidomycosis it seems logical to proceed with desensitization of the patient with coccidioidin, followed by the administration of iodine therapy *Martin* and Smith have developed a program for desensitization in cases of blastomycosis (This method has been described previously in the section on the treatment of Blastomycosis) Among various types of iodine therapy, potassium iodide has been most extensively used The writer considers ethyl iodide inhalation therapy more logical, since it is a more direct route and a greater concentration can be obtained The initial dose is 1 5 cc (3 gm), *this is increased by* 0 5 cc (1 gm) per dose until 3 cc (6 gm) is reached A dosage of 4 cc (8 gm) has been used in some cases The amount may be given in fractional doses during the day or at one sitting To avoid cumulative effect, inhalations

are given on 2 successive days and then omitted on the third day A discussion on contraindications and possible complications is presented in the following section on treatment of Moniliasis

Roentgen Therapy This is useful only in aiding the absorption of the exudate in the granulation process and in the relief of pain It is therefore valuable as a supplementary treatment Intensive or semi intensive dosage may be used

Vaccinotherapy Supplemented by injection of colloidal copper vaccine has been reported effective by Jacobson He recommends a special extract of the organism prepared by mixture of equal parts of the filtrate from a broth culture and the filtrate from the macerated organisms The coccidioidin is injected cutaneously every 8 to 14 days depending on the degree of local and constitutional reactions The colloidal copper is given as intragluteal injections in dosages of 5 cc every 4 to 7 days depending on systemic reactions Jacobson does not mention the number of injections required This probably depends on the course of the disease

Miscellaneous *Gentian violet* is highly toxic and should be used cautiously administered intravenously in 0 25 per cent solution The total dose should not exceed 5 mg of the dye per kilogram of body weight

Antimony and potassium tartrate were used by Guy and Jacob and by Tomlinson and Bancroft in combination with roentgen rays and the results were reported good The authors recommend from 2 to 8 cc of a 1

is

capsule form and given in daily doses of 1 to 6 gm locally This remedy may be applied as a 33 3 per cent solution in olive oil

Immunotransfusion has been used but its value is doubtful Goldstein and McDonald treated 2 patients with high titer convalescent blood with resulting improvement

Surgery Surgery in the form of incision and drainage of abscesses with concurrent use of penicillin to minimize secondary infection can be undertaken with impunity Surgical removal of fungating cutaneous lesions may be done with good results It is obvious however, that removal of such lesions exerts no influence on the fundamental course of the disease The treatment of patients with pulmonary cavities is still in an unsettled stage Such patients are apparently immune to dissemination evidence of the local spread of the fungus from the cavities to adjacent pulmonary tissue has not been demonstrated Most cavities ultimately heal spontaneously There is a difference of opinion whether or not active treatment such as pneumothorax thoracoplasty, or lobectomy should be used even when the cavities persist for a long time

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HISTOPLASMOSIS

(Ret culo endothel al Cytomycos s)

No specific therapy for histoplasmosis has had a fair trial since most of the cases have been diagnosed post mortem and the few cases treated have been diagnosed late in the course of the disease It is therefore essential that a diagnosis of histoplasmosis should be considered in the differential diagnosis in patients with anemia leukopenia cachexia intermittent pyrexia lymphadenopathy and splenomegaly

Iodides Iodides in any form have not proved effective therapeutically

Arsenicals Fowler s solution potassium arsenite, arsphenamine, neoarsphenamine and mapharsen have had no effect on the course of histoplasmosis

Other Drugs Bismuth quinine and pent-

nucleotide, with or without supplementing liver, iron, or vitamins, have not proved effective in changing the course of the disease to a favorable outcome

Antimony. Meleney recommends the antimony preparations such as antimony sodium tartrate, the trivalent *organic compounds* such as fuadin, or the pentavalent preparation such as stibamine glucoside (neostam) Mantel, Troy, and Kendall report clinical *improvement in one case treated with* neostam

Sulfonamides Curtis and Grekin report a proved case of histoplasmosis treated with sulfadiazine orally, 6 gm daily up to a total dose of 576 gm All lesions cleared, but organisms were still demonstrable in sections at discharge The authors report a second proved case in which the patient recovered completely except for chronic lymphostasis The last biopsy specimen did not reveal the organism This patient received a total of 522 gm of sulfadiazine in 87 days The second case is a good example of possible favorable therapeutic results with sulfonamides in cases diagnosed early before dissemination takes place Baliña et al reported the arrest of the disease in one case of mucocutaneous involvement with the administration of sulfonamides orally and the local application of this drug Although these reports sound encouraging according to the literature there are still more failures with sulfonamides than good therapeutic results

Penicillin The therapeutic results reported with the use of penicillin have not been favorable Seabury and Drygas observed no response to penicillin therapy in 2 cases Davis and Neff describe 2 failures with the use of penicillin Similar *reports* have appeared

Surgery I believe that in a case in which the lesion is accessible and isolated before *dissemination has taken place surgery* should be of value I have had no opportunity of determining whether desensitization with histoplasmin vaccine is necessary before surgery *is undertaken* However, because of the close relation between the micro organisms of *Blastomyces dermatitidis* and *Histoplasma capsulatum* as evidenced by the cross immune reactions, one would deduce that desensitization in hypersensitive cases would be advisable *just as it is in* blast cosis

Roentgen Rays The reports indicate *the roentgen ray is* not an effective t peutic agent in histoplasmosis

cc, sulfonamides or neostam Every e should be made to diagnose the disease and thus to start treatment before dissen *tion has taken* place

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MONILIASIS

The treatment of moniliasis at best is too successful Newer and more effec treatment is necessary It is my belief t successful therapy will depend on the covery of new agents, which through eit stimulation of immune reaction or dir fungistatic or fungicidal action will br about a cure of a disease that at present most resistant, particularly in its generali cutaneous and systemic types

For the sake of simplicity treatment will

ough investigation of the diet, hygiene, parathyroid disease, and diabetes is essential

LOCALIZED TYPES CHRONIC PARONYCHIA It is essential to instruct patients of the danger to their hands in frequent immersion in water, especially dishwater, and that they should avoid handling unwashed vegetables and fruits It is advisable to protect the hands with cotton and rubber gloves if dishwashing and the handling of fruits and vegetables are necessary

Local treatment consists of warm soaks in a saturated solution of boric acid for 10 to 15 minutes, morning and night, followed by the application of the following ointment 2 per cent mercurochrome crystals, 4 per cent water, and 6 per cent salicylic acid with the addition of vaseline and lanolin Greenwood and Rockwood recommend the application of sodium perborate paste morning and night

Roentgen therapy has proved effective in doses of 50 to 75 r, unfiltered In my opinion this treatment is effective not because of its fungistatic and fungicidal action but because of its effect on chronic inflammatory tissue

EROSIO INTERDIGITALIS BLASTOMYCETICA This condition may occur alone or may accompany chronic paronychia The protec-

vised The local treatment found most effective is the use of warm boric acid solution compresses followed by the application of a 5 per cent solution of mercurochrome Bacterial fuchsin solution (1 per cent) may be used instead of mercurochrome Treatment is carried out twice daily

VESICULOPUSTULAR AND ECZEMATOUS MONILIASIS The local treatment is as follows Any one of the following ointments may be found effective, being applied once or twice daily

Ointment	*Per cent*
(1) Bacterial fuchsin	1 0
Zinc oxide	6 0
Starch	6 0
Vaseline (*qs ad*)	
(2) Mercurochrome crystals	2 0
Water	4 0
Salicylic acid	3 0
Vaseline	
Lanolin (*āā, qs, ad*)	
(3)* Caprylic acid	10 0
Diethylene glycol monoethyl ether	3 0
Carbowax (6000)	47 5
n propyl alcohol	10 0
Zinc caprylate	5 0
Sodium hydroxide	2 45
Water	22 05

* Obtainable from Mycoloid Laboratories Little Falls, N J

The amount of sodium hydroxide may vary since enough is added for adjustment to a reaction of pH 8 0

The last ointment has been used successfully and reported by Keeney

INTERTRIGENOUS MONILIASIS Obesity, diabetes and mechanical and physical factors causing heat, moisture, and maceration in the folds as well as poor hygiene, should be considered and corrected whenever possible The local treatment is the same as that advised above for erosio interdigitalis blastomycetica

PERLECHE In all cases of perlèche the possibility of a dietary deficiency, particularly riboflavin deficiency, should be considered Poorly fitting dentures, producing mechanical irritation and a good soil for prolific growth of *Candida albicans*, which normally occurs in the mouth, should be corrected

Locally, the application of an ointment made up of 2 per cent salicylic acid, 2 per cent sulfur precipitate, and petrolatum is helpful

I have found cauterization with a hot needle or a fine high frequency spark effective as a supplementary treatment

INTRA ORAL THRUSH When this condition is seen in infants, the source of infection may be a monilial vaginitis in the mother, or a chronic paronychia, or erosio interdigitalis blastomycetica in the mother or the nurse maid Malnutrition is another underlying cause These factors should therefore be considered in the treatment of thrush in infants In older children and adults the condition is more resistant It may be part of the symptom complex of systemic or generalized

cutaneous moniliasis It may be associated with a systemic disease such as diabetes malnutrition or parathyroid dysfunction Investigation and correction if possible are therefore essential for good treatment

The local treatment is not too satisfactory, especially when intra oral thrush is part of a generalized cutaneous or systemic moniliasis In these cases local therapy at best gives only temporary relief The following local treatment has been tried and is recommended

(1) Sodium perborate (3 dr to ½ glass of water) as a mouth wash three times a day

(2) Gentian violet (1 per cent aqueous solution) painted on the involved areas once a day Treatment should be stopped if there are any signs of irritation

The sodium salts of propionic valeric caprylic capric and undecylenic acids are fungistatic and fungicidal in varying degrees for the different pathogenic fungi when tested in vitro Of these fatty acid salts sodium caprylate is particularly effective against *Candida* (monilia) *albicans* Keeney therefore recommends a 20 per cent aqueous solution of sodium caprylate adjusted to a reaction of pH 7 4 applied to the lesions in the mouth every 2 hours with swabbing of the entire mouth twice daily My experience with 2 cases of intra oral thrush associated with cutaneous and onychial involvement did not parallel those reported by Keeney However more cases need to be treated before a correct evaluation of the effectiveness of such treatment can be made

Autogenous vaccine therapy has not been successful in my experience

VULVOVAGINITIS Systemic causes such as diabetes and deficiency diseases as well as local gynecologic causes should be looked for and corrected wherever possible Vulvovaginitis may be associated with generalized cutaneous or systemic moniliasis the treatment for which is discussed below

The local treatment as recommended by Alter et al consists in the application of a jelly like mixture of 20 per cent equal parts of calcium and sodium propionate in a tragacanth base and buffered at a reaction of pH 6 5 The following is a good formula

Drug	*Per cent*
Calcium propionate	9 5
Sodium propionate	9 5
Propionic acid	1 0
Glycerin	10 0
Betonite	32 0
Water	38 0

Gentian violet douches diluted 1 10 000 given three times a week or less frequently if there is any sign of irritation are of value Lewis recommends a vaginal suppository (0 13 gm to each) Hesseline employs Lugol s solution diluted to one-quarter each night two capsules containing a mixture of potassium iodide and potassium iodate (6 2 parts of potassium iodide to 1 part of potassium iodate) Capsules of 00 to 000 are employed The drugs are diluted and mixed with kaolin so that each capsule contains about 0 125 gm of the iodides

In our experience the best results in cases of localized vulvovaginitis have been obtained with 1 per cent bacterial fuchsin solution painted on twice a day and a daily cleansing douche of sodium bicarbonate (½ teaspoonful to a pint of water) The vulvovaginitis associated with generalized cutaneous or systemic moniliasis does not respond readily to local treatment

Autogenous vaccinotherapy has not proved to be successful

Generalized Cutaneous and Systemic Types There is no known effective cure for these types of moniliasis The only hope lies in the discovery of new and effective antibiotics Search for new antibiotics is being carried on in many laboratories

Therapy should be directed toward the eradication of all foci of infection Unfortunately with the present armamentarium that is almost an impossible task to carry out especially if the focus is in the gastro-intestinal tract Complete study of the patient is essential with particular emphasis on diabetes nutritional factors hygiene and parathyroid disease These studies should include roentgen examination of the chest to determine the presence or absence of bronchopulmonary involvement

A high vitamin high calorie diet rein

forced by components of the vitamin B complex and liver therapy is helpful

Iodide therapy particularly ethyl iodide inhalation has proved most effective in bronchopulmonary moniliasis probably because the coefficient of distribution between the alveol
sufficiently
relatively
blood stream It has also been demonstrated that a small proportion is returned in the venous blood so that the tissues are exposed to relatively large amounts of iodine In bronchopulmonary moniliasis inhalation therapy is a more direct route The initial dose of ethyl iodide is 1 5 cc (3 gm) This

given on two successive days and skipped on the third day to avoid cumulative effect A mineral oil spray to avoid irritation of the throat may be used once a day The inhaler of choice * is designed to allow a comfortable mixture of ethyl iodide † and air to be inhaled It is important that the ethyl iodide be free from impurities particularly phosphorus This can be accomplished by proper distillation

The most common complication is the usual papulopustular eruption occurring particularly on the face and upper part of the trunk The eruption usually disappears a few days after the drug has been discontinued Treatment may then be resumed without ill effect in most cases A more severe pemphigoid eruption should be a signal to discontinue the drug and not to resume its use after the eruption has cleared since the second attempt may result fatally Peripheral neuritis should be watched for although it is a rare complication This complication is probably due to the ethyl radical If such a complication occurs treatment should be discontinued

Other forms of iodine therapy may be used Saturated solution of potassium iodide starting with 15 drops three times a day orally and increased 3 drops daily to the point of tolerance is most commonly administered Sodium iodide intravenously may be given in 1 gm doses once a day Tincture of iodine in milk or water starting with 5 drops three times a day and increasing the dose to the point of tolerance is another form of iodine therapy

Martin and Smith recommend desensitization with monilial vaccine in hypersensitive patients before any course of iodine therapy is started (The technic is outlined previously in the section on Blastomycosis)

Keeney has given sodium caprylate intravenously but the sclerosing action on the veins has made its protracted use impossible

Vaccinotherapy both autogenous and

and monilia extracts alone and in combination

Hiatt and Martin describe a dramatic recovery in a case of bronchopulmonary moniliasis treated with anti *Candida* (monilia) *albicans* rabbit serum The patient was given injections subcutaneously beginning with 0 1 cc of a 1 10 dilution and the dose was increased by 0 1 cc daily until 0 9 cc was reached The desensitization series was repeated twice This good result was obtained in a patient with a negative skin test to Candida vaccine a negative complement fixation test and a positive immediate reaction to an anti *Candida albicans* rabbit serum The writer has tried this form of therapy in 2 cases with generalized cutaneous and mucous membrane involvement without beneficial therapeutic results In one case no tests for sensitivity were done In the other the test to vidiomycin showed at the end of 48 hours an erythematous reaction slightly larger than 1 cm in diameter The reaction to anti Candida rabbit serum was erythematous and nonelevated no pseudopod was observed

This writer is using serum from patients who have recovered from chronic paronychia caused by *Candida* (monilia) *albicans* as a therapeutic agent The results and proper technic will appear in a later publication after more work has been done

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* The inhaler may be obtained from Warren Collins Boston Mass

† Purified ethyl iodide may be obtained from Burnham Soluble Iodine Company Auburndale Mass

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SPOROTRICHOSIS

Potassium Iodide This is the most effective weapon in the treatment of this disease It is administered orally, beginning with 10 drops of a saturated solution three times a day and increasing by 3 to 5 drops per dose daily until tolerance is reached—usually 30 to 40 drops three times a day This maximal dose is maintained Potassium iodide is best given in water or milk This treatment should be continued for at least 1 or 2 months after apparent complete recovery If this drug is not tolerated orally, sodium iodide in daily doses of 1 gm may be given intravenously

Another method of iodide therapy is by iontophoresis Shaffer and his associates reported good results with daily treatment for a total of 13 weeks They used a strong solution of iodine U S P diluted 1 100 in isotonic solution of sodium chloride and increased to 1 50 after 7 weeks Since the active ion, iodine, is an anion, the negative electrode was attached to the involved parts and the indifferent positive electrode was placed on the back The current was about 15 ma for 20 minutes in the first week and was gradually increased to about 35 ma for 30 minutes

In the rapidly spreading or fulminating type and in systemic sporotrichosis it is wise to administer potassium iodide orally and ethyl iodide by inhalation (The technic and dose are described in the section on Actinomycosis)

Iodide probably does not act as a direct fungicide Cure may result because of the stimulation and proliferation of fibroblastic tissue and encapsulation of the organism

Surgery Surgery and cauterization are contraindicated because such procedures are frequently followed by prolonged suppuration and ulceration and retard rather than effect a cure However, in cases of fluctuation, incision and drainage may have to be attempted *Aspiration of the pus* may be adequate and should be tried first

Miscellaneous *Roentgen therapy* to local lesions is a useful supplement in semi intensive dosage with filtration

Autogenous and stock vaccine has not proved its value, but in resistant cases may be used in conjunction with iodide therapy

Sulfonamides have been employed with good results in some cases

Penicillin and streptomycin have not produced good therapeutic results in this disease The results obtained with iodide therapy far surpass those in patients treated with the known antibiotic agents

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MADUROMYCOSIS

Since maduromycosis (Madura foot, mycetoma) may be caused by a variety of fungi belonging to different species no one specific drug is effective Iodides, thymol, copper sulfate, and antimony compounds are not helpful Sulfonamides and penicillin are useful indirectly in taking care of the usually present superimposed bacterial infection which is frequently the cause of death and directly in cases caused by actinomyces (The dosage and course of treatment are discussed in the section on Actinomycosis) *Conservative surgery, such as excision* of localized early lesions, or radical surgery, *such as amputation* in the more extensive cases, may be necessary

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GEOTRICHOSIS

Cases of bronchopulmonary geotrichosis have been reported Oral and intestinal forms of the disease have also been de scribed Since species of Geotrichum are frequently found in the mouth and intestinal tract of normal persons caution must be used before this organism is blamed for producing disease The writer and his co workers have grown pure cultures of Geotrichum from the stools of patients with ulcerative colitis as compared with few scant colonies from the stools of normal persons and from those with diarrhea from other causes

[illegible]

Ethyl iodide inhalation therapy is advisable in the pulmonary type Rest and a high vitamin intake are as essential as in any other systemic disease Pulmonary tubercu losis must be ruled out before any iodide therapy is instituted

Oral geotrichosis may be treated with sodium perborate (3 dr to ½ glass of water) as a mouth wash Gentian violet, 0 5 to 1 per cent aqueous solution, painted on the involved areas, may prove effective Conant et al suggest gentian violet diluted 1 10 000 in 10 per cent alcohol, painted on involved areas and supplemented by gargling with a 1 100 000 solution of the dye The gentian violet treatment should be repeated daily for 4 to 5 days and then stopped to avoid irritation of the mucous membrane

JACOB H SWARTZ

RICKETTSIAL DISEASES

The human infections discussed in this chapter are caused by micro organisms called rickettsiae in honor of H T Ricketts, who first observed these pleomorphic cocco bacillary forms and who died of a rickettsial infection acquired in his studies of its eti

[illegible]

tions in man but also occur as parasites of various arthropods and animals The rickett sial diseases of man are classified into five groups

(1) Typhus fever
(2) Rocky Mountain spotted fever
(3) Tsutsugamushi disease (scrub typhus)
(4) Q fever
(5) Miscellaneous unrelated infections (trench fever etc)

The prevention and treatment of the more important infections in the first four groups are considered in this section

Prevention THE TYPHUS FEVER GROUP *Epidemic Louse Borne Typhus* Recent de velopments in methods for active immuniza tion of man and for control of human lice have taken this disease from the ranks of the major epidemic scourges of mankind It is now possible to produce adequate quantities of potent vaccine in several ways In the United States Cox vaccine is preferred, it is derived from yolk sacs of developing chick embryos All persons who are likely to be exposed to epidemic louse borne typhus should receive a primary course of vaccine consisting of two subcutaneous injections of 1 ml each The National Institutes of Health of the United States Public Health Service specify the potency which must be attained in epidemic typhus vaccine in the United States

Evidence from laboratory and field studies clearly indicates that Cox vaccine reduces the mortality of epidemic typhus almost to zero and lessens the severity of the illness, the duration of fever the number of compli cations and the period of convalescence It is probable, moreover that vaccinated per sons are less likely to contract the infection than unvaccinated persons although this point has not been clearly established Stimu lating doses of 1 0 ml each should be ad ministered subcutaneously at least twice a year to all persons who are continuously ex posed to louse borne typhus

Reactions to vaccination against typhus

generally consist of mild local redness of 1 or 2 days duration In exceptional cases there may be a slight rise in body temperature and malaise with slight headache for 2 or 3 days It is important to note that the physician must always determine whether his patients are sensitive to egg protein before he administers any type of vaccine derived from chick embryos A few severe allergic reactions have been recorded and 2 fatalities occurred when egg vaccines were administered to persons with definite histories of sensitivity to egg proteins

More spectacular than vaccine in its effect in preventing epidemic typhus is the recently developed method for control of human lice Dichloro diphenyl trichloro ethane or DDT as 10 per cent powder in talc or other inert material is lethal to lice Millions of louse infested persons have been successfully deloused by DDT dust blown into their hair down their necks up their sleeves and into their undergarments either with hand operated dust guns or larger compressed air devices Clothes which have been properly treated with 10 per cent DDT dust remain lethal for lice as long as a month or more DDT does not kill the rickettsiae of typhus consequently every patient with epidemic typhus should be carefully bathed with 1 per cent lysol solution on admission to a hospital and subsequently dusted with 10 per cent DDT powder once a week until discharged The patient s garments should be disinfected promptly by heat to kill both lice and typhus rickettsiae All hospital personnel handling typhus cases should be immunized ... and rubber gloves in ... tient onc ... infect his ... cised in drawing blood however since rickettsiae are present in the blood during the febrile period

Murine Typhus Fever Although a similar vaccine is available against the relatively mild disease murine typhus fever its use is recommended only for laboratory or field workers who are continuously exposed to the rickettsiae of murine typhus In communities where this disease has its highest incidence the attack rates are not great enough to justify community wide immunization programs More can be accomplished by measures to control rats and fleas The use of 10 per cent DDT dust on rat runs reduces the rat flea population to a low figure and probably also reduces the incidence of murine typhus in man

Brill s Disease This mild form of typhus is not known to be associated with lice fleas or rats The etiologic agent appears to be closely related to classic epidemic strains of typhus and consequently one might expect epidemic typhus vaccine to have some protective value but this has not been studied Since the incidence of the disease is low the use of vaccine in the attempt to prevent Brill s disease is not justified

THE ROCKY MOUNTAIN SPOTTED FEVER GROUP *Rocky Mountain Spotted Fever* It is recommended that all persons who plan to visit areas where they may be exposed to infected ticks should be vaccinated with Rocky Mountain spotted fever vaccine prepared either from the tissues of infected ticks or from yolk sac membranes The potency of these vaccines is regulated by the National Institutes of Health A primary course of two or three subcutaneous inoculations of 0 5 to 1 ml each should be followed each season by a single stimulating dose The evidence concerning the use of vaccine over a 20 year period in the Rocky Mountain area clearly indicates its value both in reducing the incidence of Rocky Mountain spotted fever in exposed persons and also in lessening the mortality and clinical severity of the illness The precautions described in the paragraph ... nce of ... in ... ared from yolk sacs

Methods for the control of ticks are not satisfactory DDT is effective against ticks only when excessively large amounts are employed Risk of contracting Rocky Mountain spotted fever from ticks can be reduced by certain precautions (1) careful inspection of the entire body twice daily when walking in tick infested areas and prompt removal of any ticks (2) use of tweezers rather than bare fingers in removing ticks (3) avoidance of contact with feces or coxal fluid of attached ticks

Rickettsialpox This mild illness has been recognized only in New York City but the house mouse and the mite responsible for its

presence occur in many other cities Preventive measures consist of eliminating house mice

Recent reviews on the Rocky Mountain spotted fever group have been published by Cox

TSUTSUGAMUSHI DISEASE GROUP *Tsutsugamushi Disease or Scrub Typhus* This relatively severe infection has not been recognized in human subjects in North America During World War II several thousand cases occurred in the United States Armed forces in the South Pacific and in the Burma areas Attempts to devise a suitable vaccine using the technics which were successful for epidemic typhus and Rocky Mountain spotted fever have not yielded a satisfactory immunizing agent

Garments can be impregnated with various materials which effectively repel the mites responsible for transmission of scrub typhus to man Benzyl benzoate and dibutyl phthallate are the most suitable for this purpose

Smadel has reviewed the recent developments on tsutsugamushi disease

Q FEVER GROUP The rickettsiae of Q fever have been found in certain ticks and in cows milk but the various outbreaks of Q fever in man cannot be ascribed to infected ticks or cows milk Since the mode of transmission is not understood relatively little can be done in the prevention of Q fever Vaccination of experimental animals has been successful but no data are available on the effectiveness of vaccine in human Q fever This has been shown by Smadel

Treatment GENERAL MEASURES In the care of patients suffering from the more severe rickettsial diseases (epidemic typhus Rocky Mountain spotted fever and tsutsugamushi disease) several general measures should be observed which may exert considerable influence on the course of the infection These are briefly considered in the following paragraphs

Good nursing care is essential Complete bed rest should be enforced The patient should be moved in his bed frequently to lessen the hazard of necrosis of the skin Cold applications may be essential to keep the body temperature from rising above 104° F The disorientation and stupor which are usually present in severe rickettsial infections result in a state of helplessness which requires constant attendance by the nursing staff during feeding and elimination Incontinence of urine is a troublesome complication which may require an indwelling catheter during the acute phase of the disease The rectal temperature and pulse rates should be recorded at intervals of 4 hours and the blood pressure at least once daily

The diet should contain 3000 to 4000 calories for an adult with a protein content equivalent to 25 gm of nitrogen for a patient of 150 pounds For the more seriously ill patient a fluid diet is preferable and in some instances it must be given by tube Nourishment is best administered in frequent small feedings during the day and once at night The intake of sodium chloride should be restricted if edema or oliguria occurs

Fluids should be administered orally or parenterally in amounts adequate to produce a urine output of at least 1500 ml in 24 hours In patients with high temperatures as much as 4 liters of fluid may be required daily The fluid intake and output as well as the specific gravity of the urine should be charted daily particularly in cases with oliguria and/or azotemia The occurrence of renal failure in a severe rickettsial infection is a bad prognostic sign A fall in systolic blood pressure below 80 mm Hg may be the first indication that oliguria and azotemia are imminent When these appear they usually last from 1 to 4 days before the patient either succumbs or the blood pressure rises accompanied by an increase in the urinary volume The judicious use of intravenous plasma human albumin or whole blood in this critical period of severe hypotension may be expected to aid the recovery of some patients The use of intravenous sodium chloride solutions is hazardous for patients with oliguria although the hypotension which accompanies oliguria may be temporarily alleviated by saline infusions edema frequently ensues This is a serious complication associated with a high mortality In this connection it should be recalled that there usually is a reduction in serum albumin in the acute stage of the more severe rickettsial diseases

Chloral hydrate or paraldehyde is preferred for the control of active delirium or extreme

restlessness Barbiturates may increase the delirium and should be avoided Relief from headache may be obtained by the administration of codeine in doses of 30 mg at intervals of 3 hours Morphine should be used only with extreme caution in the more severe rickettsial infections Antipyretic drugs are of doubtful value and may be harmful Digitalis preparations are rarely indicated The administration of oxygen may be of value in the treatment of tsutsugamushi disease and should be used whenever patients exhibit cyanosis

To combat the secondary bacterial infections which may occur in severe rickettsial infections antibiotics such as penicillin and streptomycin should be used depending on the sensitivity of the organisms encountered Sulfonamides appear to have an adverse effect on rickettsial infections their use is contraindicated in the acute stage of a rickettsial infection

Specific Therapy Before the outbreak of World War II the only specific therapeutic measures for rickettsial diseases which offered any promise were those employing the immune serum of man or animals Beneficial effects were obtained only when the serum was administered in the first 3 or 4 days of the illness Serotherapy now has been supplanted by several chemotherapeutic agents and antibiotics which favorably affect the course of rickettsial infections not only in experimental animals but also in human subjects These various compounds are discussed by Findlay and Snyder This section considers chloramphenicol aureomycin terramycin and para aminobenzoic acid

Chloramphenicol (Chloromycetin) This antibiotic has given favorable results in the treatment of the various rickettsial diseases Its chemical structure is known and it has been shown to be effective in synthetic form The drug is administered in capsules by mouth The dosage schedule for rickettsial diseases is as follows an initial dose of 40 to 50 mg per kilogram of body weight (this may be divided into three parts and given at hourly intervals) at intervals of 4 hours thereafter a maintenance dose of approximately 10 mg per kilogram until the temperature has been normal for 24 to 48 hours It is not necessary to determine the concentration of the antibiotic in the blood Clinical improvement usually occurs rapidly and body temperature returns to normal in 36 to 72 hours Chloramphenicol is not toxic in the doses employed No change in red or white blood cells attributable to the antibiotic has been reported

Aureomycin Several clinical trials have indicated the beneficial effects of aureomycin in the various rickettsial diseases The oral route is preferred but the antibiotic is also available for intravenous administration The recommended schedule is an initial dose of 20 to 30 mg per kilogram of body weight, followed by a maintenance dose of 10 mg per kilogram of body weight every 4 hours until the temperature has been normal for 2 or 3 days No important toxic effects have been noted other than gastro-intestinal irritation Clinical improvement usually has been prompt

Terramycin This antibiotic is effective experimentally against the pathogenic rickettsiae and preliminary reports of clinical trials are favorable The dosage is similar to that for aureomycin

Para-aminobenzoic Acid (PABA) This substance is more difficult to administer than the antibiotics mentioned above and does not give beneficial results as promptly Its use is recommended only when the antibiotics are not available Careful attention must be paid to details of administration as emphasized by Snyder and associates

Summary of Specific Therapeutic Agents A direct comparison of chloramphenicol aureomycin and terramycin in human rickettsial infections has not been reported Further clinical evidence is necessary before the physician can logically choose between these antibiotics The evidence available at present suggests that PABA is more difficult to administer properly and less rapid in its action than the antibiotics, but PABA may be used when these are not available

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BARTONELLA DISEASE

(OROYA FEVER AND VERRUGA PERUANA)

These two conditions are considered as different manifestations of the same process Another name is Carrión's disease It is endemic in South America especially in Peru and Colombia

In the acute stage or Oroya fever period treatment must be directed toward the rapidly developing anemia Hodgson has emphasized the importance of frequent transfusions of whole blood and advocates 500 to 700 cc of blood daily during the period of rapid blood destruction Large doses of penicillin or streptomycin may also be of value in cutting down the incidence of secondary infections Howe believes that hyperimmune rabbit serum containing a high titer of agglutinins for *Bartonella bacilliformis* may ameliorate the course of the disease but is of no value prophylactically The dose of the serum is 10 cc intravenously every other day until a total dosage of 50 cc has been administered Other than supportive measures there is no other specific form of therapy

In the chronic or verruga stage excision of the large necrotic nodules may be necessary with careful attention to hemostasis The prognosis as to life in the chronic stage is excellent whereas the mortality rate in the acute period ranges from 30 to 50 per cent

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PROTOZOAN DISEASES

LEPTOSPIROSIS

The treatment of leptospiral infections is unsatisfactory Fortunately many of them tend to be mild illnesses without jaundice among these are "swamp fever" or marsh fever (*Lept grippotyphosa*) 7 day fever of Japan (*Lept hebdomadis*) 7 day fever of Australia (*Lept pomona*) and the variously named fevers caused by *Lept bataviae Lept rachmat Lept salinem Lept bovis Lept suis Lept febrilis Lept autumnalis* and others Illness varies greatly with all strains but that due to *L icterohaemorrhagiae* (Weil's disease) tends to be most severe attended with jaundice in fully half the

cases and with a mortality rate from 4 to 48 per cent Canicola fever (*Lept canicola*) usually pursues a milder course

Treatment of severe leptospirosis due to any species of leptospira is the same as that accorded patients with Weil s disease it is largely symptomatic Dehydration from vomiting is relieved by intravenous liquids containing glucose When possible a high carbohydrate high protein intake is advisable The tendency to bleed may be combated by vitamin K parenterally Transfusions of blood should be given when indicated *Sedatives and opiates may be used* as required although the severe embarrassment of liver and kidneys should be borne in mind Damage to the kidneys resembles that following hemolytic transfusion reactions hence the oliguria and anuria are doubtless due to the same kind of renal failure recognized in 'lower nephron ne

anuria have suggested use of lyophilized plasma intravenously High spinal anesthesia has been recommended probably irrationally as an extreme measure to relieve anuria Meningitic symptoms can be relieved only as they arise

Specific treatment includes the use of antibiotics and antisera Penicillin offers just enough promise to warrant its use early and in high dosages Specific antisera have been disappointing in their effects When they are available and suited to the strains responsible *they may help in any event the serum* should be polyvalent and given early and in large doses 60 cc per day intravenously for 5 days is required Convalescent serum has been warmly advocated as well as transfusions of immune blood but the numbers reported on are small

Other measures have not been proved Streptomycin has been tried in experimental infections with some success although it seems *to be weaker than penicillin* perhaps combined treatment with penicillin and serum will be in order A recent report by Heilman indicates that aureomycin is of definite value in experimental leptospiral infections This drug may prove to be of clinical value after further investigation Many chemicals have been mentioned from time *to time in treatment* arsphenamine hexamine sodium tartrobismuthate yatren and others have all been tried and abandoned. The singular resistance of *Leptospira to the* arsenicals antimonials and the current metallic and nonmetallic drugs as well as to the sulfonamides suggests that a new category of drugs especially suited to Leptospira must be discovered before leptospiral diseases can be managed

Prophylaxis is important The patient s excreta should be sterilized Vaccination with killed Leptospira from cultures is recom*mended in endemic areas Most important is* eradication of the rat Contact with rats and with all substances polluted with their urine and feces should be avoided Leptospira are able to live freely in the slime of sewers and mines in the waters of canals and swamps and in the gurry of fish wharves Waters need not be visibly polluted to support Leptospira hence epidemics among bathers have frequently been reported

Henry R Jacobs

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MALARIA

Etiology as Related to Treatment The organism *responsible* for malaria is a protozoan of the class Sporozoa and genus Plasmodium There are several species that occur naturally in monkeys birds and reptiles although none of the human species of parasites is known to produce a sustained infection in any of the lower animals Only one species *P knowlesi a parasite of monkeys* has been found by inoculation to be pathogenic to man There are four known species that infect man *P vivax* which causes vivax malaria (tertian benign tertian) *P malariae* which causes quartan malaria *P falciparum* which causes falciparum malaria (malignant tertian *estivo-autumnal*) *P ovale* a much rarer species which causes ovale malaria a mild variety *clinically similar to vivax malaria*

By the bite of an infected mosquito, sporozoites enter the blood stream of man and probably pass through an exo-erythrocytic (cryptozoite) cycle in the macrophages of connective tissue or in the endothelial cells of the liver, spleen, and bone marrow After this cycle is completed—the length of time depending on the species of plasmodia but usually being less than 10 days—the para-

32 daughter cells are formed, the number depending on the species During growth, the parasite absorbs the hemoglobin of the red cell, and hematin pigment is deposited A typical malarial paroxysm of chills and fever occurs when the adult parasites rupture the red cell membrane The free parasites then attack fresh red blood cells This asexual cycle is repeated at regular intervals —48 hours for *P vivax*, 72 hours for *P malariae,* and approximately 36 for *P falciparum* After about 10 days of asexual development, the sexual forms, which are known as gametocytes, appear in the blood stream

Further development of the parasite oc

[illegible]

way to a female gametocyte, hovering about until one eventually penetrates and fertilization occurs The unsuccessful ones immediately seek a new mate The fertilized form, or ookinete, passes between the cells of the mosquito's stomach wall and encysts on its outer surface Here the sporozoites develop in countless numbers and, on maturity, the cysts rupture and the sporozoites are released in the body cavity of the mosquito From here they migrate to the salivary gland and await the opportunity to continue their development in the human host following the bite of the infected mosquito In vivax and falciparum malaria, the first ring forms appear in the red blood cells of the host 10 to 14 days after the bite of the mosquito In quartan malaria, the incubation period is longer—18 to 25 days

Immunology. The immunology of malaria is an important consideration in the therapy of the disease In animal and human malaria, the immunity of the host is an infection immunity Once the infection has been completely eradicated, there is only a transient resistance to reinfection There is relatively little cross immunity between the different species of human malarial infections Actually, many strains exist within each species of the human malaria parasites that are immunologically distinct or different Since malaria has a great tendency to relapse, in endemic areas the occurrence of an acute infection after treatment may be either a relapse or a new infection

The species themselves differ markedly in their immune phenomena For example, falciparum malaria, the most virulent of all types and the one likely to prove fatal if not vigorously treated, has a low relapse rate, in general, probably less than 5 per cent When a relapse does occur, it is usually within 4 or 5 months following the initial infection and there is rarely more than one relapse Thirty per cent or more of vivax infections, depending on the strain, will relapse in spite of quinine or atabrine The variety of vivax malaria acquired in the Southwest Pacific seems to be the most tenacious yet encountered and 4 years after the end of World War II there remain many relapsing cases, some of which were acquired early in the [illegible]

detected following transfusions since the infected individuals suffer relatively mild or no ill effects from the disease Practically all cases of malaria which have been reported in the literature 10 or more years after initial infection without opportunity for reinfection in the interim, are proved to be of the quartan variety

Since the eradication of these infections by chemotherapy does not leave the individual with a permanent immunity, the physician must decide whether it is preferable to attempt a cure or merely to suppress the clinical manifestations of the infection

One other important point in connection with immunology of malaria concerns vaccines and specific therapy There is no experimental evidence which indicates that

there will ever be a successful vaccine Although specific protective antibodies have been demonstrated in experimental animals and man the use of antisera for therapy has not been shown to have any practical value

Objectives and Principles of Malaria Therapy The selection of drugs or regimens of therapy for the treatment of malaria is dependent on a number of considerations The most important are the prevalence of malaria in the area, the kind or kinds of species of parasites involved, whether one is dealing with permanent or temporary populations whether the physician is thinking of the individual or the community, and the potentialities of the different drugs

The aims of therapy can be classified under the following headings

(1) Causal prophylaxis or the destruction of the sporozoites injected by the mosquito before they can initiate an infection

(2) Suppressive therapy In this instance, the drug is administered to prevent the development of clinical attacks but will not destroy the infection

(3) Treatment of the acute attack

(4) Curative therapy

At the present time it is doubtful if there are any true causal prophylactic drugs that will destroy sporozoites before they undergo development and initiate an infection except in the case of falciparum malaria In this type, quinacrine, chlorguanide, and perhaps several other drugs if taken in adequate amounts for a sufficient period of time, will serve as true prophylactics

Suppressive therapy probably will be employed more extensively in the future since the newer compounds are apparently as effective as quinine and quinacrine and are less troublesome to administer For the individual or for larger groups, such as troops prisoners labor forces suppressive drugs such as chloroquine and camoquin can be given once weekly with complete success During World War II the writer was responsible for the care of several thousand cases of chronic malaria which were assigned to the hospital because of inability to combat the infection successfully In one study there were over 500 men suffering relapses at approximately 6 week intervals and a blood survey revealed that over 30 per cent were positive When they were given 0 6 gm camoquin weekly, no further relapses occurred and parasites were found only in one individual who had previously had a splenectomy following spontaneous rupture. Large scale studies in the field are currently under way to determine the relative merits of the various suppressive drugs in keeping a community free from clinical malaria and also to learn if transmission of the disease can be interrupted

The treatment of the acute attack, whether an initial episode or a relapse, usually presents no difficulties Delayed or inadequate treatment allows some infections to progress until dangerous symptoms appear Falciparum malaria usually responds promptly to therapy, its reputation for severity results from delay or temporizing The maxim to follow in the acute attack is to select the drug of choice and to be certain that amounts are given to insure high blood levels as rapidly as possible

No drugs could be relied on for curative action in chronic malaria until the recent discovery of pentaquine and other 8 amino quinoline compounds Although further evaluation is necessary, current investigations are extremely promising

Quinine Quinine has long been the standard remedy for vivax malaria, in fact, its antipyretic qualities have been known for centuries It is thought that Cinchona bark from which quinine is derived was introduced into Europe about 1640 from South America, where it had been used in the treatment of fevers in general Supposedly, the name Cinchona was applied to the bark after it had been used to cure the Countess del Chinchon wife of the governor of Peru of an attack of fever

As the value of Cinchona bark infusions became known, all readily available sources of the natural bark were soon depleted and this led to the fraudulent substitution of similar appearing inactive compounds Soon, however the Dutch transplanted young seedlings to the East Indies where improved horticultural methods and favorable climatic conditions led to the commercial development of high yielding strains In 1820 the active ingredient was discovered to be in the bark as an alkaloid which could be crystallized At the present time, there are approximately 20 such alkaloids, all possessing

antimalarial activity but quinine is used almost exclusively because of its high therapeutic effect and low toxicity It had been the aim of the organic chemists to synthesize this valuable drug but little or no success was obtained until 1944 when Woodward and Doering showed that it could be produced synthetically The process is so difficult however that it has only academic interest

Until World War II quinine retained its role as the number 1 antimalarial drug in spite of competition from some of the synthetic compounds such as quinacrine and plasmochin, which were discovered within recent years

Quinine is a protoplasmic poison and probably inhibits some of the intracellular enzymes Some believe that it alters cellular membrane permeability but its exact mode of action is unknown In malaria there seems to be a direct action on the parasite although when the parasites are mixed with solutions of quinine in vitro they can tolerate many times the concentration of quinine possible to obtain in the human body and yet they retain their viability When given in excessive amounts the drug is toxic producing tinnitus and deafness and if injected intramuscularly it may result in sloughing Occasionally an individual is found who is sensitive to the action of the cinchona alkaloids but such sensitivity is rare and is easily recognized by the extreme reaction such as cyanosis dyspnea urticarial rash vomiting and fever

As a treatment for malaria quinine must be considered from two standpoints namely as a suppressive and as a treatment of the acute attack It is difficult if not impossible to cure malaria with this compound Many infections appear to be eradicated following its use although they are usually those strains with a low relapse rate As a suppressive agent it fails to prevent the acquisition of the infection although clinical symptoms will not appear as long as the drug is used Quinine perhaps has its greatest usefulness against falciparum malaria although it is highly active against all four species of human parasites

Quinine should be given by mouth in the form of the salt either sulfate or chloride whenever possible Absorption is rapid and there is little reason to administer it parenterally except in cases of coma or pernicious vomiting When given parenterally it should be in the form of the dihydrochloride salt well diluted in saline solution since intravenous solutions if too concentrated, result in thrombosis of the veins

DOSAGE Five grains of quinine taken daily by mouth are usually sufficient to prevent the development of clinical symptoms although as stated above quinine will not insure an individual against the development of a subclinical infection

For the acute attack in adult males the author prefers to use a total of 2 0 gm of quinine sulfate during the first 24 hours in order to obtain a high concentration of the drug early in the infection This is to be followed by 5 grains (0 3 gm) three times daily for the next 5 days and then 10 grains (0 6 gm) daily for 2 weeks The total duration of treatment does not seem to influence the relapse rate There are many different quinine regimens which are claimed to result in reduced relapse rate although when investigations with adequate controls are substituted no such claims have been substantiated It has been found that strains and species of parasites respond differently to therapy which accounts for the varying results and claims In any event therapy should not be discontinued until the patient has had 5 days of normal temperature with negative blood smears

For undersized individuals or children the dose can be reduced accordingly Although quinine is known to stimulate uterine musculature it should be given to pregnant women with malaria since miscarriages are more likely to result from the untreated infection than from the use of quinine The parenteral dosage should be 10 grains of *quinine dihydrochloride* in at least 50 cc of saline given slowly This dosage should be repeated every 6 hours until relief is obtained and the patient is able to tolerate the drug by mouth

Quinacrine (*Atabrine*) During World War I the Germans lost their quinine-producing colonies and began vigorous attempts to synthesize an antimalarial compound This was finally accomplished by Mietzsch and his colleagues in 1930 when quinacrine, a synthetic crystalline dye was discovered to

have potent antimalarial properties It was *introduced into the* United States shortly after but never gained popularity until World War II when it was used on a large scale because of the limited supply of quinine

Quinacrine is an acridine dye and goes under many names throughout the world Effective against all forms of the malaria parasite, it may be considered comparable *to quinine from all standpoints* except one It has relatively little effect on the gametocytes of falciparum malaria However, it seems to be more effective than quinine as a suppressive drug in this type of malaria Fairley and his associates in Australia demonstrated that quinacrine, when given prophylactically prevented the development of *falciparum infections* The drug is absorbed rapidly and almost completely from the gastro-intestinal tract It is degraded slowly, hence it is retained for a long period of time

Dosages When used as a suppressive agent, 0 1 gm of quinacrine per day, taken for 6 successive days, is adequate For the acute attack, however, it is advisable to give 1 gm of oral quinacrine during the first 24 hours in order to obtain a high level of the *drug in the blood stream* This should be given at the rate of 0 2 gm every 5 hours Thereafter, 0 1 gm three times a day for 5 days is usually sufficient As in the case of quinine, therapy should not be halted until there has been a minimum of 5 days during which the patient is free from fever and has negative blood smears The use of quinacrine has several disadvantages One is the fact that patients become yellow colored as the result of the deposition of the drug in the skin *Another is that many individuals* develop gastro intestinal symptoms Occasionally a quinacrine psychosis has been reported This, however, is extremely rare

If the patient is unable to take the drug orally, it should be administered intramuscularly since the intravenous use occasionally results in collapse The intramuscular dose is 0.2 gm every 5 hours until 1 gm has been given and then 0 2 gm daily until oral administration can be resumed

Pamaquin (Plasmochin) Pamaquin is a synthetic 8 amino quinoline compound developed in the German laboratories in 1924 It was highly regarded *when first* used because it was thought to reduce the number of relapses Also it was highly effective as a gametocidal drug However it is extremely toxic and can cause methemoglobinemia, cyanosis, vomiting hemoglobinuria, and even circulatory collapse Because of the narrow range between therapeutic *effectiveness and* toxic dosage, its use was discontinued by the armed services during the last war Pamaquin *alone is* ineffective for the treatment of the acute attack and, therefore, when used it was usually combined with quinine as a pamaquin compound

Dosage The dosage is ⅙ grain (0 01 gm) by mouth three times daily for 4 days When used as a pamaquin compound, the drug is combined with quinine at a ratio of 0 1 gm *pamaquin to 1 0 gm of quinine Since more* effective derivatives with less toxic effects have been discovered, the use of pamaquin is not recommended

Pentaquine An intensive effort was made during World War II to discover a compound which was therapeutically more effective and less toxic than pamaquin In the 8 amino quinoline group, pentaquine, (8 [5 isopropyl aminoamylamino] 6 methoxyquinoline), also known as *SN 13,276,* has been studied in *animals and man for its toxic effects* and therapeutic value There is little doubt but that it is an improved compound in both respects In experimental animals and in man the pharmacologic activity is similar to that of pamaquin, the drug being rapidly and completely absorbed from the gastro intestinal tract Maximal plasma levels are [illegible] and it

50 to 75 per cent as toxic as pamaquin but possesses considerably more therapeutic activity When administered in nearly the *maximal tolerated dosage, 120 to 180* mg daily, it has been experimentally demonstrated to be a true causal prophylactic agent in mosquito induced vivax *malaria* South west Pacific Chesson strain When used alone in lesser amounts pentaquine will suppress fever and prevent the appearance of parasites in the blood stream, however to prevent relapses it must be used with quinine Alving and co-workers found that volunteers infected with the Chesson strain of South west Pacific malaria had a relapse rate of

67 per cent with standard remedies whereas a relapse rate of only 4 per cent was encountered when treatment consisted of 60 mg of pentaquine and 2 0 gm of quinine daily for 2 weeks This result is more significant when it is pointed out that the patients were treated at the time of their initial infection or first or second relapse before there was opportunity for the development of specific immunity All patients were hospitalized since some toxic symptoms occurred with this dosage of pentaquine

Patients with prolonged malarial infections exhibit considerable specific immunity a factor of importance when considered from a chemotherapeutic standpoint Therefore it was thought possible to reduce the dosage of pentaquine by one half and still maintain its therapeutic value This was proved in 186 ex servicemen who had experienced repeated attacks of malaria many for as long as 5 years These men had been repeatedly treated with various antimalarial compounds but their infections had not been eliminated A cure rate in excess of 90 per cent was shown on the initial treatment with pentaquine following a 2 year post treatment period of observation Proof of cure consisted of absence of relapses in addition to increased body weight and loss of such subjective symptoms as headaches

The toxic reactions associated with the greater dosage (60 mg) in the experimental studies of Alving were methemoglobin formation and in many subjects anorexia and abdominal cramps However when pentaquine was used at 30 mg daily there were few or no symptoms of any concern in the ambulatory patients There was no effect noted on the blood cells The most frequent subjective complaint was abdominal cramps

Pentaquine is the drug of choice where curative action is indicated Its curative value has been demonstrated in acute and chronic vivax malaria Its value in falciparum and quartan malaria remains to be determined

Recommended Dosage Schedule and Administration For the patient with chronic vivax malaria pentaquine should be administered orally in three divided doses of 10 mg each for 14 days With each dose of pentaquine 10 grains (0 6 gm) of quinine sulfate should be given for the same period If relapses occur the regimen should be repeated This dosage schedule has been utilized in adults of average size

When administered to individuals belonging to the dark skinned races vigilance should be exercised in anticipating hemolytic crisis even though this complication may be extremely rare Signs and symptoms of cinchonism are not to be regarded as indications for withdrawal of the drug unless they are those of a true sensitivity such as rash, cyanosis etc

Currently additional 8 amino quinoline compounds are being investigated and preliminary results indicate that a closely related compound may be more active than pentaquine Available data however are too meager to be recorded

Chloroquine (*SN 7618 and Aralen*) and Camoquin (*SN 10751*) Chloroquine (7 chloro 4 [4 diethylamino 1 methylbutylamino]quinoline) and camoquin (4 [7 chloro-4 quinolylamino] a diethylamino o cresol) are two synthetic antimalarials developed during the intensive research program conducted under the auspices of the National Research Council in various institutions during World War II In every respect these compounds seem to be superior to quinine and atabrine when used suppressively or for the termination of the acute attack A great deal of investigation remains to be done before these drugs can be completely evaluated but the studies conducted to date have resulted in a consistent demonstration of their superiority This is particularly true of chloroquine These drugs are almost completely absorbed by the gastro intestinal tract and toxic symptoms rarely occur in the prescribed dosage In experimental malaria of lower animals the therapeutic index is much greater than that of quinine or atabrine In human malaria both chloroquine and camoquin are extremely effective against all species of parasite the important usage will probably be for suppression since 2 tablets taken once weekly are sufficient to suppress all attacks of malaria even in highly endemic areas However the rapidity of their action indicates a widespread use for treatment of the clinical attack It is hoped that the ease of administration and the almost complete freedom from unpleasant symptoms when used in small amounts for suppression would re

duce the number of effective human carriers so that transmission would not occur Investigations of this possibility are now being conducted by public health authorities

DOSAGE The recommended dosage for suppression is 2 tablets each containing 0 25 gm chloroquine diphosphate (equivalent of 0 15 gm of base) taken on the same day of each week For the acute attack the initial dose is 1 0 gm (4 tablets) to be followed by 0 5 gm (2 tablets) after 6 hours On the second and third days 0 5 gm (2 tablets) are given making a total of 2 5 gm (10 tablets) in 3 days Although not necessary 2 tablets can be given daily thereafter for 5 successive days

Paludrine (*Chlorguanide*) Paludrine the English proprietary name for a biguanide antimalarial drug 1 (p chlorophenyl) 4 iso propylbiguanide was discovered by English workers in 1945 It is a white compound relatively nontoxic Its chief advantage lies in its apparent wide range between the toxic level and the effective therapeutic dosage Like quinacrine quinine and the 4 amino quinoline compounds the usefulness of paludrine except in falciparum malaria is in the suppression or treatment of the acute attack it has no effect on the relapse rate nor on *P vivax* or *P falciparum* gametocytes

One of the chief disadvantages of paludrine is that it fails to relieve parasitemia or fever as quickly as the drugs discussed above Magraith reports in some cases the persistence of fever for as long as 4 days after the onset of therapy In some of the experimental malarial infections particularly gallinaceum in birds a high degree of drug resistance was encountered which persisted through mosquito passage The parasite retained its susceptibility to other antimalarial compounds

USE AND DOSAGE The author believes that more convincing evidence is needed before this compound can be recommended in preference to the 4 amino quinoline compounds for suppression or treatment of the acute attack If used for suppression the recommended dose is 100 mg twice weekly For the acute attack of vivax malaria 100 mg three times daily should be given for 2 or 3 weeks Paludrine can be given parenterally in doses of 150 mg intravenously every 4 hours

Other Antimalarial Agents Methylene blue arsenic bismuth sulfonamides and a few other compounds possess some antimalarial activity However when compared with the drugs described above these compounds cannot be recommended As stated convalescent serum known to contain specific antibodies has relatively little effect on the clinical course of the disease

Supportive Therapy All malaria cases should be kept in bed when possible in spite of the fact that this infection is treated in an ambulatory fashion throughout most of the world The diet should be light and contain plenty of carbohydrates Only fluids preferably those containing glucose should be administered during the fever Fruit juices are beneficial Patients should be kept warm during the chill and sponge or alcohol baths should be given to relieve high fever Aspirin 0 6 gm can be given for the severe headaches which however usually disappear with rigor During convalescence iron and liver should be given for anemia In the uncomplicated cases all nonspecific measures should be directed toward keeping the patient comfortable without overtreatment

LOWELL T COGGESHALL

BLACKWATER FEVER

The etiology of blackwater fever one of the most serious tropical illnesses remains unsolved The condition is recognized as a complication of chronic malaria or as being associated with that infection

Blackwater fever is almost invariably associated with falciparum infections Those reports claiming the vivax malaria parasite as the sole cause lack convincing proof for the absence of *P falciparum* The onset of the hemoglobinuria is frequently attributed to quinine This has never been substantiated but it was noted by Foy in Greece that the high incidence of blackwater fever dropped markedly during World War II when quinine was not available and this was in spite of a marked increase in the number of malaria cases On the other hand Foy also reports that Hippocrates gave a precise description of malarial blackwater fever centuries before quinine was used as a medicinal agent Fairley reported a similar decrease in the incidence of blackwater fever in the Pa

cific area when quinacrine was substituted for quinine However, he believed the reduction was associated with the disappearance of falciparum malaria since quinacrine is more effective as a curative compound

Renal failure is a constant feature of the more severe cases of blackwater fever and relative impairment of function is always present It is almost certain that the anuria and oliguria are not the result of blockage alone Undoubtedly renal ischemia plays an important role

Treatment. The treatment of this disease is that for any individual with sudden hemolysis and impairment of kidney function It is possible to find innumerable regimens recommended as important in the treatment of blackwater fever However, when sufficient cases are treated to permit valid evaluation, there is remarkably little difference in the mortality rates Since there is some suggestive evidence that quinine is detrimental and since there are other drugs equally efficacious if not more so, the use of quinine should be discontinued immediately Incidentally, parasites frequently are absent from the blood stream during the acute attack The patient should be kept warm and not moved more than necessary Nitrogen and chloride balance should be maintained, especially in cases with vomiting In replacing the loss of blood, no effort should be made to maintain a normal red cell count since the toxemia damages the heart and an excess of blood volume can result in right heart failure Small frequent transfusions are advisable Sodium citrate by mouth is recommended, administering 8 gm initially and 4 gm every 2 hours until the urine is alkaline Sedatives to prevent restlessness are advised, particularly barbiturates

The prognosis of blackwater fever is always grave, the mortality rate averaging about 50 per cent over the world If recovery is attained, the patient should be removed from malarious areas

LOWELL T COGGESHALL

RELAPSING FEVER

(African Tick Fever Tick Fever Spirillum Fever)

The relapsing fevers due to spirochetes of the genus Spirochaeta (Borrelia) are similar clinically, the distinctions based on epidemiologic differences depend perhaps as much on the nutritional state of the patient as on the virulence of the organism Thus epidemic European relapsing fever, which is louse-borne, tends to be more severe and causes a

tick borne variety is a sporadic disease not associated with social upheaval However, the species of Borrelia involved are dissimilar serologically Several have been identified *Bor recurrentis* (European relapsing fever), *Bor duttonii* (tropical relapsing fever), *Bor novyi* and *Bor turicata* (American), *Bor persicum* and others The tick-borne variety is transmitted to man by the bite of "soft" ticks of the genus Ornithodoros An extraordinary feature is the transmission of the spirochetes through the egg from mother tick to its young, so that the infection may be maintained in ticks alone Endemic foci may therefore persist without the help of vertebrate infection The term "tropical" relapsing fever should not divert attention from the fact that endemic foci exist in Arizona, Colorado, Texas, California Kansas, Oklahoma, and in Canada, and that cases continually appear in those places

The natural tendency in the majority of cases of relapsing fever of the tick borne variety is toward spontaneous cure, if the patients are otherwise healthy and strong Without treatment of any kind, specific or otherwise, the disease runs its relapsing course and then disappears in most instances A considerable immunity remains after an attack Nevertheless, desperate illness results from relapsing fever at times The plan of care of the patient, and the assessment of effectiveness of specific therapy alike, must take into account the importance of the patient's own natural resistance It is imperative to arrive at diagnosis promptly and to begin specific treatment at the earliest moment because early treatment insures the best outcome An important part of treatment is the support of the strength of the patient High fever must be controlled by frequent and thorough sponging A liberal intake of water must be established The severe headache should be alleviated by

0 6 gm aspirin given freely and by the use of 30 mg of codeine when required When the course mounts to a crisis before specific therapy can be started all specific treatment must be withheld to avoid precipitating a fatality the crisis must be weathered as best it can with help from digitalis caffeine morphine intravenous liquids ice packs and restraint during delirium

Neoarsphenamine Neoarsphenamine has been thought specific and curative and although it has proved remarkably effective in numerous cases it fails to eliminate the infection in all according to some workers Failure has been variously attributed to resistance shown by strains of the organism and to insufficient treatment Nevertheless neoarsphenamine remains a potent agent It should be given intravenously in doses of 0 3 to 0 9 gm according to body weight the total amount required estimated as 0 1 gm per kilogram of body weight It is best (1) to give the first injection at the beginning of a febrile rise (2) to give more than one injection (3) not to give any drug when a crisis is imminent

The remarkable susceptibility of the spirochetes of relapsing fever to arsenicals and *the mildness of the disease in many instances have given rise to the most diverse opinions* as to the amount of drug required and how it should be given Some say that a single dose of 0 03 to 0 5 gm of neoarsphenamine is sufficient to cure 80 per cent of cases *others insist that each case should receive* 0 1 gm of neoarsphenamine per kilogram of body weight given in several injections of 0 6 gm each There are still others who mistrust the curative powers of neoarsphenamine *and have resorted* to bismuth preparations such as potassium bismuth tartrate or bismuth salicylate All agree that the arsenicals should be given with care Severe vomiting frequently follows an intravenous dose The commonest reaction is exacerbation of the already severe headache and a rise in fever Sometimes the temperature rises 4 to 7° and the clinical state of the patient deteriorates alarmingly death during such a reaction is not a rare *occurrence It is* especially dangerous to give arsenic to a weakened patient who has already suffered two or more severe febrile cycles In these patients who obviously need treatment most urgently, it is best to await the beginning of the next relapse (next febrile cycle) meanwhile supporting the patient by sponging sedation and adequate water intake and then to begin treatment at the *onset of the* next episode with a small to moderate dose of neoarsphenamine Fortunately these patients may now be treated better with penicillin

The *intervals between injections in* a course of neoarsphenamine treatment are

give *succeeding doses at subsequent febrile* onsets whereas others proceed with regular intervals of 3 to 5 days between doses It seems advisable in the absence of definite evidence to the contrary to attempt a cure with a regular *schedule of injections*

In spite of the apparent vulnerability of the spirochetes to neoarsphenamine and mapharsen cases will occur in which cure is not achieved Worse still certain individuals *are entirely refractory to arsenicals* In these instances penicillin should be employed

Penicillin Penicillin will doubtless attain the dominant position among the drugs useful *against relapsing fever as has been noted* by Fischer and Taft It seems a fortunate circumstance that the spirochetal diseases rat bite fever syphilis yaws and relapsing fever should all yield to penicillin as well as to arsenic so that one or the other of these drugs may be employed at will Penicillin has a great advantage over arsenic in that it is a safer drug to use The curative power of penicillin in relapsing fever compares favorably with that of neoarsphenamine As with the arsenical drugs treatment with penicillin must be begun with care for the rapid destruction of large numbers of spirochetes may *release dangerous amounts* of spirochetal products and will invite unnecessary complication from anaphylactoid reactions related to the Herxheimer phenomenon The caution advised in the use of neoarsphenamine *should therefore be exercised* with penicillin The first dose of penicillin *should be given at or before the onset* of fever thereafter succeeding doses may *follow* in regular succession until the projected course has been finished As with neoarsphenamine the earlier treatment is begun

the better the outcome Penicillin may be given intravenously or intramuscularly, ordinarily the intramuscular route is adequate The literature does not specify how little penicillin will suffice for cure but it seems likely that 30 000 to 50 000 units every 3 hours or comparable amounts of longer acting preparations (procaine penicillin) constitute effective practice and that this be kept up for at least a week The clinical state and the rate of diminution of the size of the spleen should be considered indexes of progress It will be wise to continue treatment until cure seems certain and somewhat beyond so that needless trouble from later relapses is forestalled

A recent report by Heilman indicates that aureomycin is of value in the treatment of experimental relapsing fever

HENRY R JACOBS

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RAT BITE FEVER

Two distinct diseases are called rat bite fever and have been described in the literature by Witzberger and Cohen Altemeier et al Swyer and Wheeler The first sodoku (cat bite fever) usually is associated with rat bite fever or with the bite of animals that worry rats and is due to *Spirillum minus* (*S morsus muris*) the second which may follow rat bite but also occurs in epidemic form through contaminated food (Haverhill fever) is due to *Streptobacillus moniliformis* (*Haverhillia multiformis Actinomyces muris ratti*)

Spirillum minus infections respond well to arsenical drugs Neoarsphenamine given intravenously in four to six injections of 0 3 to 0 6 gm is curative in the majority of cases Mapharsen is also effective It is necessary to remember that severe reactions may accompany arsenotherapy of this disease, and even though two to three injections are given it is prudent to administer two or three more to prevent relapse The first injection should be made at the beginning of a fever cycle An occasional case will require a course of eight or 10 injections at weekly intervals before it yields and exceptionally arsenotherapy fails altogether Recently penicillin has been reported on favorably by Altemeier et al If these early reports are substantiated penicillin will displace the arsenical drugs completely Apparently the spirilla are susceptible to penicillin for 15 000 to 20 000 units every 3 hours intramuscularly for 5 days is curative

Streptobacillus moniliformis infections yield readily to penicillin This is fortunate for they resist all other treatment A full course of 200 000 to 300 000 units a day for 5 to 7 days is almost certainly adequate and perhaps a less intensive schedule will do

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TOXOPLASMOSIS

Up to the present time no effective agent to combat clinical toxoplasmosis has been discovered Warren and Sabin have studied the effect of antiprotozoal drugs in experimental animals and found that in mice sulfathiazole has a definitely beneficial effect Weinman and Berne have also shown that in acute experimental infections the sulfonamides may be of value but that they have no effect on the carrier state Because of these laboratory studies sulfathiazole has been used in human cases but the results have been disappointing Penicillin has been shown to be of no value

In chronic toxoplasmic chorioretinitis the usual forms of therapy for chorior

should be carried out Foci of infection must be removed adequate rest enforced and in well chosen cases induced fever with typhoid vaccine may slow down the inflammatory process

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LEISHMANIASIS

(Kala azar Trypanosom as s)

Positive diagnosis should be made before treatment is begun and special care should be taken not to mistake the organisms of *Histoplasma capsulatum* for *Leishmania donovani* in bone marrow studies Treatment of kala azar makes use of two classes of drugs (1) organic antimony compounds and (2) diamidine compounds The antimonials are older and have proved their effectiveness through the years the diamidines are newcomers which promise great usefulness

The Antimony Compounds Tartar emetic is the oldest antimony compound used against kala azar It is still employed because of its cheapness Its toxicity and undependability have stimulated the discovery of more desirable compounds and at present greater reliance is placed upon pentavalent antimonials of lower toxicity and better performance

Neostibosan (ethyl stibamine Bayer 693B von Heyden 693) is the antimonial of choice certainly for the occasional case according to Most and Lavietes It is the least toxic it may be given intramuscularly or intravenously and it may be depended on to achieve what an antimonial can in kala azar The initial dose is 0 1 gm dissolved to make a 25 per cent solution given intravenously the second dose is 0 2 gm and all subsequent doses are 0 3 gm Injections are given daily or every other day until a total of 4 5 to 5 0 gm has been administered In children depending on their age smaller individual doses are used but the total amount employed should be at least 2 0 gm Sometimes cure is not reached under this schedule treatment should then be continued with doses of 0 3 gm until a total amount of 8 to 10 gm has been given

Solustibosan (antimony V gluconate antimony hexonate stibatin stibanose stibogluconate) is well regarded by some workers although reports of failures by others will doubtless make this drug seem untrustworthy It has a low toxicity to recommend it so that large doses may be given intravenously or intramuscularly Perhaps when a higher dosage schedule is followed solustibosan will become recognized as a dependable preparation It is supplied in ampules ready for use Early reports stressed the efficiency with which solustibosan eradicated fever and illness and the rapidity of apparent cure later ones expressed disappointment over the number of relapses Vigorous treatment somewhat like that recommended by Sen Gupta and Chakravarty should be employed when solustibosan is used The total dosage is calculated according to body weight 4 cc per pound for children 3 cc per pound for adolescents and 2 cc per pound for adults Intravenous injections are given daily not to exceed 10 cc in the child 15 cc in the adolescent and 20 cc in the adult The total amount for any person in one course should not exceed 220 cc of the drug Solustibosan has also been used in an oily suspension given intramuscularly at longer intervals

Stibosan has been extensively employed by some workers It is more toxic than neostibosan A course of treatment comprises 10 to 15 injections of 0 2 gm given intravenously every second or third day Very ill patients should be started with 0 05 gm and continued with slightly higher amounts according to tolerance Young children should begin with 0 025 gm per dose increased slowly to 0 1 gm adolescents may be started with 0 15 gm, increased to 0 2 gm per dose

Stibosan is effective but its capacity to produce anaphylactoid reactions makes it less desirable than neostibosan and solustibosan

Urea stibamine (stiburea) has been popular in India Although it is an effective drug it is unstable Furthermore its antimony content and hence its toxicity varies Its important advantage is that it is inexpensive which makes it useful in mass treatment The standard dosage is 2 0 to 2 5 gm given intravenously every 2 to 3 days beginning with 0 05 gm per dose and increasing by 0 05 gm each time until 0 2 to 0 4 gm is given per injection A course of treatment requires a month or longer

Neostam (stibamine glucoside) is given intravenously every other day beginning with 0 2 gm and continuing with 0 3 gm until 15 doses have been given

The choice of antimonial to be used depends on several factors When cost may be ignored the best to be had is neostibosan (or solustibosan) because of its low toxicity and dependable effectiveness and because it has few peculiarities of behavior Other members of the group are also effective but they are better left to persons of large experience or reserved for special situations A late arrival among the antimonials anthiomaline has been reported upon favorably When expense is the determining factor in the choice urea stibamine and tartar emetic will have to be used The use of antimonials is attended with risk of death to the patient in some series a death rate during treatment of 5 per cent has been reported Certainly fatalities cannot be ascribed to the drug in every case but the implication is plain when neostibosan consistently holds the lowest death rate The first danger is that due to idiosyncrasy of the patient and this should be tested for carefully at the outset The second is due to anaphylactoid reactions shortly following injections these reactions are especially common after tartar emetic A third resembles anaphylactic shock and it appears after injections late in the course of treatment When a course is finished jaundice may develop The antimonials should therefore be used with care certainly the least dangerous drug that can be afforded should be chosen Giddiness and nausea alone shortly after an injection especially of tartar emetic need not be taken too seriously Patients with pulmonary tuberculosis advanced heart disease nephritis or grave liver diseases should never receive antimony In these patients if treatment must be given one of the diamidines should be used certainly a trial with stilbamidine or pentamidine may be risked if tuberculosis complicates kala azar

The Diamidine Compounds In recent years a group of nonmetallic drugs has been found effective in the treatment of leishmaniasis all are diamidines and those reported upon are stilbamidine pentamidine propamidine and phenamidine Stilbamidine is most effective but pentamidine will doubtless become most popular The use of stilbamidine invites the risk of producing diamidine stilbene (stilbamidine) neuropathy which is due to damage to the central nervous system most often manifested by anesthesia and paresthesia of the trigeminal nerve areas Oaster and Fidler cite lesions that have been found in the brains of dogs treated with this drug Stilbamidine is a

posed to light and air it quickly becomes toxic and dangerous to use In spite of great pains one may encounter anaphylactoid reactions These drawbacks make stilbamidine seem a treacherous drug yet because it may be used when antimonials are forbidden or when they have failed it will have a definite use in the treatment of kala azar Pentamidine and the others of this group are less toxic but also less effective

Stilbamidine (stilbamide M & B 744) freshly dissolved in newly distilled water is given intravenously in 1 per cent solution every day beginning with 25 0 mg and increasing to 50 to 75 mg according to tolerance but never more than 1 mg per kilogram of body weight The injection should be made slowly The alarming and troublesome reactions yield to adrenalin most of them may be avoided by giving a small dose of adrenalin just before the injection With careful attention to the preparation of the solution for injection much difficulty can be averted A course consists of 10 injections although several more may be needed to pro

duce the desired effect as described by Wilner and Haedicke

Pentamidine (pentamidine isethionate) is also supplied by May and Baker Ltd It has the great advantage *over stilbamidine in not* being nearly so toxic The drug is given intravenously in doses of 75 to 100 mg every day for 12 to 15 days

The complications of kala azar must be treated specifically whenever possible Malaria, intestinal worms dysentery, amebiasis, avitaminosis, and undernutrition should be dealt with adequately Cancrum oris in children responds well to penicillin parenterally and to mild local measures during antimony treatment Sepsis due to bacteria must be combated vigorously with penicillin, streptomycin and sulfadiazine Complications *arising from antimony itself usually subside* when treatment is stopped The frightening anaphylactoid phenomena respond well to *adrenalin, but once they appear treatment* should stop If tartar emetic or urea stibamine was responsible, further treatment with neostibosan may be possible

Treatment of kala azar should continue until clinical and histologic cure is reached In India kala azar seems to respond better to treatment than it does in Africa, according to reports, but resistant and relapsing cases will appear in any series

Dermal Leishmaniasis Three clinical varieties of cutaneous leishmaniasis can be distinguished (1) post kala azar dermal leishmaniasis, often regarded as a benign outcome of kala azar, (2) oriental sore, or eastern cutaneous leishmaniasis, (3) western cutaneous leishmaniasis, or mucocutaneous *leishmaniasis*

Oriental sore usually heals by itself In any event it runs a mild course without danger to the patient except when unusual complications appear When a single sore is present it may be treated locally with berberine sulfate in 2 per cent solution injected under and around *the ulcer Atabrine* similarly given has been credited with rapid cures Local applications of tartar emetic, sulfa drugs, and penicillin have been recommended The sores should be kept clean and protected with bandages for they may be [illegible] by flies carrying the agents of [illegible]s, phagedenic ulcer, *and sepsis In* addi[illegible] to local measures, a course of neostibosan given in the manner described for kala azar may prove helpful

Western mucocutaneous leishmaniasis is another matter This disease (forest yaws *espundia, uta, Chiclero ulcer*) may attack the mucous membranes of the nose, mouth and pharynx with the production of painful eroding ulcers causing great deformity and debility Effective treatment is therefore more urgent than in the other varieties of dermal leishmaniasis The antimonials are employed much as they are in kala azar more recently fuadin (stibophen), a trivalent antimonial, has gained preference over the pentavalent compounds Fuadin *is given* intramuscularly in courses of 15 to 25 injections, twice a week in doses beginning with 0 5 cc and increasing to 5 0 cc When necessary, *fuadin may be* given every *other day* in the same amounts

Organic arsenic compounds such as di*oxydiaminoarsenobenzol (Eparseno) or neo*arsphenamine, are also helpful in espundia Local treatment of lesions on the mucous membranes is important because bacterial activity contributes to the destruction The ulcers should be cleansed twice daily with mild antiseptic washes Penicillin locally and parenterally *should be used when required* Each ulcer should be anesthetized with cocaine solution and coated with powdered potassium antimony tartrate and bandaged Some physicians recommend injecting emetine hydrochloride in 2 to 5 per cent solution around and under the ulcers, daily for 4 to 5 days, being careful *not to use more* than 60 to 75 mg of emetine per day Berberine sulfate in 1 to 2 per cent solution may be used instead The outlook for cure is good [illegible] *fol* [illegible] ith [illegible] ith [illegible] ms [illegible] its use in prophylaxis

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AFRICAN TRYPANOSOMIASIS
(African Sleeping Sickness)

Before beginning specific treatment of sleeping sickness coexistent diseases and undernutrition should be dealt with whenever possible so that the patient may better endure the potent drugs to be given him

Bayer 205 (germanin suramin belganyl moranyl Fourneau 309 antrypol maphuride) is a white stable powder readily soluble in water It is injected intravenously in doses of 1 0 gm dissolved in 10 cc of water once a week until 10 0 gm have been given Owing to the remarkable capacity of trypanosomes to become resistant to the drug many workers prefer the doses at shorter intervals The drug is well tolerated but the urine should be examined repeatedly to detect early damage to the kidneys A first test dose of 0 3 gm should be employed to detect idiosyncrasy

Tryparsamide (orsanine Fourneau 270) is the drug that must be used after the trypanosomes have entered the central nervous system It is given intravenously in 1 to 4 gm doses in courses of 10 to 15 weekly injections the total amount of the drug for a course being 0 045 gm per kilogram of body weight Treatment should be pushed to the limit of safety because trypanosomes acquire resistance to arsenicals with comparative ease An interval of 2 to 3 months of rest may be followed by a second course if cure was not achieved in the first attempt

Combined treatment is usually recommended A preliminary course of Bayer 205 is followed by a course of tryparsamide after 2 to 3 weeks rest Whenever tryparsamide is employed attention should be paid to the eyes because optic neuritis and blindness threaten susceptible patients Unfortunately the most careful watching may not avert disaster since signs of damage might not appear until after treatment is finished Premonitory symptoms are dimness of vision pain lacrimation and photophobia

Recently the diamidines stilbamidine, pentamidine and propamidine have attracted favorable attention Stilbamidine appears to be less valuable than pentamidine and propamidine Pentamidine isethionate is given intravenously in 8 to 12 doses of 50 to 100 mg each propamidine isethionate likewise in doses of 50 to 75 mg each Both are effective in early cases These diamidines are also useful in prophylaxis 5 0 mg of either drug per kilogram of body weight intramuscularly in a single dose protects against the disease for 5 to 6 months according to van Hoof et al The diamidines may be used in combination with tryparsamide Harding has reported his experience with 2 713 cases treated with the drugs described

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SOUTH AMERICAN TRYPANOSOMIASIS
(Chagas Disease)

Unless penicillin proves to be useful the chemotherapy of Chagas disease will remain unsatisfactory Hitherto specific treatment has made use of Bayer 7602 (AC) or the British preparation M 3024 of the same drug said to be diallyl malonyl di (-4 amino 2 methyl quinonyl 6 amide) which has been described by Fulton This drug is given intramuscularly every 5 to 7 days in doses of 8 to 12 mg per kilogram of body weight Great improvement has been reported from its use but because the course of the disease is frequently erratic amelioration may not have been due to treatment alone Recently

during 2 days

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reported on The remarkable cardiotropism of *Schizotrypanum cruzi* results in acute or chronic myocarditis which frequently becomes fatal Myxedema from destruction of thyroid gland tissue may be treated with thyroid extract

Prophylaxis requires eradication of the bug vector by sprays of gammexane DDT or pyrethrum and improvement of housing to make habitations bug proof

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mony medication such as nausea and vomiting shortly after administration sore gums joint pains anorexia and malaise throughout the course appear frequently and may become severe

Fuadin is more acceptable than tartar emetic It is given intramuscularly only It is available in ampules and is stable The first dose is 1 5 to 3 0 cc The second dose is 5 0 cc 2 days later Thereafter 5 0 cc are given three times a week until 40 cc have been given in all The injections cause little pain and toxic reactions are uncommon

Anthiomaline is another antimonial that has been used with success It also comes in ampules and is stable It is given intramuscularly three times a week in 3 cc doses

GRANULOMA INGUINALE

Granuloma inguinale is best treated early as described by Greenblatt Robinson and Marshak and Rodriguez Certain diagnosis rests upon finding the pathognomonic Donovan bodies in the lesions of the disease and since the measure of success of treatment and the test of cure depend alike on microscopic examination of specific material it is prudent to apply skill in the technic in this art Formerly specific treatment depended almost exclusively on the antimonials fortunately streptomycin has been found to be more effective, certainly in production of immediate results and recent evidence indicates that aureomycin may become the treatment of choice Success is more certain with an early start

Antimonials The antimony compounds bring quick results in early granuloma inguinale Tartar emetic is the oldest of this group of drugs It is given intravenously in 1 per cent solution every 2 or 3 days in ascending doses The first dose is 1 cc (A much smaller test dose should be given first to forestall trouble due to idiosyncrasy) Each succeeding dose is 1 cc larger until 10 cc are reached then the dosage is decreased by 1 cc each time until only 1 cc is given Following a rest period of 2 weeks the whole course of treatment is repeated Freshly prepared solutions are preferred to older ones The toxic manifestations of anti

in any event treatment should be continued until healing is complete and satisfactory After healing has taken place weekly doses should be continued for 6 months to prevent recurrences

Other antimony preparations are available for use in granuloma inguinale although they have had less application than the three mentioned above Antimony sodium thioglycollate antimony thioglycollamide and diramin have been used Of the three Greenblatt et al claim that diramin will probably become most popular In general the antimonials produce their best effects when given early in the disease In spite of intensive treatment however certain cases become resistant especially to tartar emetic in some further progress may be made through use of fuadin anthiomaline or diramin and a cure may be achieved After the disease has become chronic the likelihood of cure through chemotherapy lessens

When a stubborn case is found a search should be made for Vincent s organisms in the lesions This complication should be removed by local application of neoarsphenamine after cleansing the lesions with hydrogen peroxide and by giving hot sitz baths and by applying 20 per cent podophyllin in olive oil daily until the granulations disappear Local anesthetics are applied first if this treatment is too painful Scarlet red ointment should then be em

ployed to stimulate healing This regimen is recommended for all cases by Tomskey et al Continued treatment with antimony may then produce added improvement

Streptomycin Streptomycin has introduced a new and hopeful departure in the specific treatment of granuloma inguinale The early report of Barton et al gave evidence of its effectiveness this was soon followed by publications by Kupperman Greenblatt and Dienst who reported almost immediate relief of pain early disappearance of the Donovan bodies and complete involution of lesions These authors found that 4 gm of streptomycin per day for 5 days is definitely better than 2 gm per day for a longer period hence it is advisable to adhere to the heavier dosage schedule at present With 4 gm a day and a 5 day course only 1 of 51 patients required retreatment whereas with 2 gm per day or less for a period averaging 20 days there were 8 recurrences in a group of 32 patients One patient was given 4 gm a day in vaginal suppositories for 4 days with complete healing Hirsh and Taggart and others have confirmed the curative effect of streptomycin Penicillin is without effect

Aureomycin Recently Hill et al have reported excellent results in the treatment of granuloma inguinale with aureomycin Twelve cases have been treated successfully At the start of treatment 300 to 500 mg of aureomycin are administered intravenously two to three times daily for 3 or 4 days This is usually followed by 50 mg intramuscularly once or twice a day for 10 days Following this period 250 mg of aureomycin three times daily are given for 10 days

These authors feel that aureomycin is superior to streptomycin in the treatment of this disease

Nonspecific Treatment Nonspecific measures designed to hasten cure and applied during specific treatment include surgical excision and radiations with roentgen rays Excision may be done when lesions are localized Radiation may be considered when the lesions are extensive the dosage should be similar to that employed in the treatment of skin cancer and only questionable benefit is to be anticipated Both measures are adjuvant and unless there is assurance that specific therapy cannot achieve cure either because of the nature and extent of the lesions or because of their chronicity or resistance they should be postponed

Each patient is to be urged to return at weekly intervals for at least 6 months after healing seems complete so that the earliest signs of recrudescence will be noted. If streptomycin was used retreatment is in order, if one of the antimonials was used treatment should continue for 6 months with a weekly dose even when nothing is found

The management of the late effects of granuloma inguinale depends on their nature Troublesome scars and large keloids may be excised if their removal promises relief

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SYPHILIS

Syphilis has been known as a disease entity for approximately 450 years Development in therapeutic agents divides this time roughly into three periods Therapy until the last 50 years was unsatisfactory and discouraging but since then advances in the knowledge and treatment of this crippling disease have appeared

The first period extended from approximately 1493 until the first decade of the 20th century Therapy in that era consisted mostly of the haphazard use of mercurials, a form of treatment which had been introduced by the Arabs because of the impression that secondary syphilis was a manifestation of scabies Since both diseases responded somewhat to such medication, little progress was made in differentiating them During the first part of the 19th century, potassium iodide was introduced and was found to hasten the resolution of some syphilitic lesions

The second period, which extended from 1903 to 1943, was marked by the discoveries of the etiologic agent of syphilis and a sero logic diagnostic test for the disease In 1905, Schaudinn and Hoffman discovered and de scribed the *Treponema pallidum,* and, in 1907, Wassermann and Bruck applied the complement fixation test to the diagnosis of syphilis The discovery of the specific etiologic agent opened the field for studies in chemotherapy and, in 1909, Ehrlich and Hata, after the 606th experiment, discovered the chemical preparation salvarsan

In 1943, the third period began with the introduction, by Mahoney and his associates, of penicillin therapy in syphilis Because of the wartime economy and all out mobilization of scientific efforts, it was possible to study the effects of this antibiotic to an extent that might never have been possible under ordinary circumstances The marked advances in treatment made possible the study of other obscure aspects of this protean disease and resulted in the development of many new concepts concerning problems of immunity, infection, and the specificity of serologic tests From the experiences gained during the past 5 years more concrete opinions have been made on the efficacy of penicillin treatment, especially in the early stages of this disease Laboratory and clinical investigations in this field are still going on unabated, largely encouraged by early successes, and it is predicted that some new [illegible]nges in therapy may be at hand before [illegible] book can be published The specific ef[illegible] penicillin may have on altering the [illegible]e of syphilis in the latter years of infec[illegible]on is still a matter of conjecture

In this section it is planned to outline specifically those advances which have resulted from the rapid treatment of syphilis with penicillin Certain detailed therapeutic re gimes will be presented which have proved effective in managing the various stages of syphilis Throughout this discussion, an at tempt will be made to integrate the more recent concepts of immunity since they are most pertinent to the problem of treatment and permit the adoption of more intelligent approach to the management of patients with syphilis The treatment schedules out lined below represent the collective opinions of most investigators and provide acceptable and effective methods of treatment No at tempt has been made to discuss the various rapid treatment methods which utilize in tensive courses of arsenical and bismuth preparations because it is felt that such methods and therapeutic results are readily available elsewhere and have no place in this treatise The combined use of heavy metals and penicillin will be discussed under the appropriate subheading

Immunity. The advent of penicillin treat ment in syphilis has renewed interest in the problem of immunity to this disease The specific problems of immunity of great im portance in the proper understanding of the fundamental biology of the infection are those concerned with clinical conditions [illegible] munity, as used here, is to be interpreted as meaning "resistance"

Natural Immunity As far as it has been determined, *syphilis is a disease* which, under natural conditions, occurs only in man Infections can be produced in certain ani*mals by experimental inoculation* and, more recently, it has been shown that other animals, such as mice, rats, guinea pigs, hedge hogs, and hamsters, *previously* thought to be completely resistant to infection, can harbor the organisms without developing any signs or symptoms of infection

Acquired Immunity The development of acquired resistance is dependent entirely on the host's previous experience with the infecting organism Experiments show, *both in* animals and man, that following the appear-

ance of the primary lesion a second chancre will not develop ordinarily after a new inoculation with *Treponema pallidum* This state was called *anergy* as described by Neisser but it is known usually as *chancre immunity* Such immunity is only relative since reinoculation of massive amounts of infectious material may result in the production of typical primary lesions The duration of this state of "chancre immunity" is open to a great deal of speculation and it has been demonstrated that patients with late syphilis general paresis and tabes dorsalis may develop chancres when inoculated with *Treponema pallidum*

Because of the development of rapid methods of treating syphilis it is now possible to interfere with the development of immunity by the patient at any phase of the disease This point is extremely important since inadequate therapy results not only in the failure to produce a "cure" but it may interfere with the patient's development of acquired immunity Such patients are vulnerable to infectious relapses neurorecurrences and treatment resistant cutaneous and precocious tertiary lesions At the present time there is no certain method either clinical or laboratory of distinguishing between relapse reinfection or superinfection in syphilis With the advent of the rapid method of treatment however a practical point must be considered If the patient with early syphilis is treated adequately and "cured" but still is permitted to circulate in his previous sexual environment he has an excellent opportunity of becoming reinfected Such situations have been noted on numerous occasions and have been designated as *ping pong syphilis* It is not necessary that the patient develop the characteristic clinical manifestations of syphilis in order to be classified as a case of reinfection *A suspicion of reinfection may arise when* the serologic titer increases after therapy

While all of the above facts are of interest academically and must be considered in interpreting failure rates a more practical approach must be taken in managing the individual patient In view of these facts it is most essential that epidemiologic follow ups be made on all of the patient's suspected sexual partners and the patient himself must be observed carefully for an adequate period of time

Artificial Immunization All attempts to produce active immunity by artificial means have been unsuccessful

Mechanisms of Immunity The mechanisms of producing immunity in syphilis remain obscure No circulating antibodies specific for *Treponema pallidum* have been demonstrated but this does not exclude their existence because virulent strains of *Treponema pallidum* have not been cultivated There is no doubt that the positive complement fixation and flocculation tests with non

for the positive serologic test may not be the antibodies responsible for immunity This assumption is based on many animal experiments However it is felt that certain of the antibodies produced in response to the spiro

propose clinical confirmation of the similarity of these antigens At this time the serologic titer is at its height and it is assumed that the patient has his greatest acquired resistance owing to the severe clinical manifestations that are noted in his skin and other organs where the spirochetes come to rest

The recent studies of Neurath and his associates on the flocculation tests for syphilis indicate that there may be a practical method for demonstrating humoral antibodies By selective chemical precipitating methods they isolated a globulin fraction from the proteins of the blood which carry the antibodies responsible for the serologic test Either by further refined fractionations or absorption or inhibition activities a more clearly defined picture may arise in relation to the immunology in syphilis

The cellular factors must play an important part in immunity against syphilis but as in other infectious diseases they cannot be evaluated because they cannot be examined objectively

Cross Immunity Clinical evidence indicates that patients with either yaws or syphilis are resistant to both diseases The degree of cross immunity is largely dependent on factors such as time and the quantities of inoculum used for testing the immunity However under conditions of natural infec-

tion the degree of cross protection appears to be significant

Serologic Tests for Syphilis Serologic tests are of great value in establishing the diagnosis of syphilis and evaluating the responses of various patients to therapy Some of the salient features and recent advances made in serologic tests will be pointed out in this section It is important first of all, to emphasize that nonspecific lipoid antigens are used in performing serologic tests for syphilis In general there are two types of tests the flocculation and complement fixation In the flocculation test the antigen is mixed with the patient s serum and the degree of flocculation read directly The complement fixation test is a more complicated reaction which requires in addition to antigen and serum an accurately measured amount of complement and a suitable hemolytic system Within the last decade various quantitative procedures have come into greater use in order to give some indication as to the amount of reagin present in the patient s serum The unit readings vary from laboratory to laboratory For uniformity therefore all designations will be indicated as dilution units i e the highest dilution giving a reaction of 2 plus or more Dilution units may be converted to Kahn units by multiplying the former by 4 The quantitative serologic technics have distinct advantages over the qualitative serologic tests, and the following chart indicates the comparative reactions given by the quantitative and the qualitative tests

Quantitative vs Qualitative Serologic Test for Syphilis

	Quantitative			*Qualitative*	
	256	Dilution	Units	Positive	
	128	"	"		
	64	"	"		
	64	"			
	32				No
Satisfactory	16			"	obvious
fall in titer	4			"	change
	8				
	4	"	"	"	
	4			"	
	4		"		

This chart of serologic tests represents a satisfactory fall in titer after therapy and compares it with the qualitative serologic test which shows no change

The value of such information in managing a syphilitic patient is quite obvious A progressive increase in serologic titer indicates progression of the disease whereas a steadily falling titer indicates a satisfactory response to therapy An increase in titer in a patient whose post therapy titer had been falling is a definite indication that the patient has had a relapse or *reinfection* Persistently low titered serologic reactions in late latent syphilis adequately treated are indications of a satisfactory course

Caution must be used in the interpretation of all serologic tests Such tests are not infallible and are to be considered as only one of the essential aids in arriving at a diagnosis A single positive reaction by itself is of no significance If the test fits in with the clinical picture or repeated tests show con

nosis and treatment

It has become increasingly evident that there are many diseases and febrile states which produce transitorily false positive serologic tests for syphilis These include such conditions as immunizations (smallpox, typhoid tetanus influenza etc) respiratory infections (chronic and acute common colds) infectious mononucleosis malaria virus pneumonia bacterial infection lymphogranuloma venereum, leprosy and a number of other conditions Positive serologic reactions with beef heart antigens are obtained also in other treponemal diseases such as yaws bejel and pinta but these reactions are truly positive in the sense that these diseases are elicited by spirochetes which are related morphologically and antigenically to *Treponema pallidum*

Method of Action of Penicillin in the Treatment of Syphilis The early studies on

penicillin It was found that penicillin differed markedly from the arsenicals in its effect on the spirochete When oxophenarsine hydrochloride is injected into a *patient* the organism and the tissues compete for the drug The combination is completed in a short interval of time, and the death or sur

vival of the spirochete is dependent on the amount of bound arsenical and the susceptibility of the particular strain of organism to the drug With penicillin however it has been shown that the therapeutic efficacy against the spirochete is enhanced enormously by merely increasing the number of injections The most striking difference between the action of these two medicaments arises in the fact that it cannot be demonstrated that penicillin is bound and concentrated by the organism Therefore the treponemicidal action of penicillin can be related to the length of time in which effective spirocheticidal levels can be maintained in the body fluids Recognition of this time factor and the necessity for maintaining an effective level is most important since it forms the basis for the fundamental differences in therapy with penicillin compared with arsenicals Eagle and associates have demonstrated that penicillin at extremely low concentrations has a definite spirocheticidal action They have shown by animal experimentation that the maintenance of blood levels greatly in excess of 0 01 to 0 2 units per cubic centimeter is wasteful of a large part of the active penicillin Studies on the optimal time interval for the administration of penicillin have yielded variable results Eagle s experimental work based on the fact that the lag phase of recovery of the spirochetal organism is apparently relatively long indicates that the exact time of each

every 3 hours was adequate for hospitalized patients

Moore and associates studied the time dosage relationships for amorphous penicillin in patients with clinical syphilis Their results showed the optimal dose to be 1 200 000 to 4 800 000 units of the drug in aqueous solution and that the total duration of treatment should be between 4 and 15 days The interval between injections should be within the limits of 2 to 6 hours Their studies with crystalline penicillin G showed in general that a total of 2 400 000 units of the antibiotic given over a 7½ day period was adequate When the penicillin was administered in absorption delaying menstrua a single daily injection of 600 000 units given for a period of approximately 10 days was as effective as the above schedule employing aqueous crystalline penicillin G In view of the above noted minimal effective levels and the increasing efficacy of penicillin as a spirocheticidal agent many of the dosage formulas presented below may seem to be markedly in excess of the necessary dose Such excesses however are on the conservative side and it is felt that they are justified because possibly an increased blood level would favor concentration of penicillin at the sit

les

of most syphilologists that penicillin causes a serious reaction only rarely

There are four possible types of reactions which may occur during penicillin therapy as follows

(1) Toxic actions (primary irritant variety)
(2) Allergic manifestations
(3) Therapeutic shock (Jarisch Herxheimer)
(4) Therapeutic paradox

The chances of a primary toxic reaction resulting from penicillin injections are relatively negligible and have been reported only in patients who have received the antibiotic by the intrathecal method. Since central nervous system syphilis responds satisfactorily to intramuscular injections there is no necessity of running the risk of a toxic reaction by the intrathecal administration of penicillin

Mild allergic reactions due to penicillin therapy are not uncommon It is estimated that they may occur in 8 to 10 per cent of the patients who are treated The allergic reactions develop most frequently following administration of penicillin in beeswax and oil The amorphous type of penicillin was much more inclined to produce reactions probably because of allergenic impurities in the mixture

Generalized reactions have been encountered in penicillin therapy with symptoms

caria Skin manifestations may be of the toxic erythema variety or eruptions of the erythematous macular maculopapular and

vesiculobullous types Urticaria occurs most frequently Fortunately in most instances the allergic symptoms may be controlled by the use of antihistaminic agents In patients with dermatophytosis flare ups of the locally infected areas as well as the production or aggravation of id reactions have been noted

Therapeutic shock or the Jarisch Herxheimer reaction is encountered frequently in the first days of therapy Approximately 40 per cent of the patients with primary and secondary syphilis will have fever which begins within 12 hours after the start of therapy and continues up to 24 hours This febrile reaction may or may not be accompanied by an exacerbation of mucocutaneous lesions Approximately 25 per cent of patients with latent or late syphilis will experience mild febrile reactions to penicillin but in most instances such reactions should not disturb the physician Jarisch Herxheimer reactions occurring in instances of heavily infected congenital syphilitic infants syphilitic infections of the upper respiratory tract and perhaps certain cases of cardiovascular and central nervous system syphilis may be serious and in rare instances terminate fatally It has been noted by some observers that a patient with unsuspected syphilis may develop when injected with penicillin for some other reason a febrile Jarisch Herxheimer reaction as well as a later rise in serologic titer

Early Syphilis In the light of current development it is now evident that penicillin alone is the treatment of choice in early syphilis *Two menstrua have been found* equally effective for administering penicillin *i e aqueous solutions and various absorp*tion delaying media When utilizing crystalline penicillin G in aqueous solution it is agreed generally that a total dosage of 4 800 000 units is adequate The dosage schedule recommended for the aqueous solution is 50 000 units intramuscularly at intervals of 2 or 3 hours for 96 injections The first plan requires 8 days and the second 12 days Clinical evaluation makes it clear that one can accomplish the same end with either the shorter or the longer period and there are vantages in *reducing the length of hos* l stay

Therapy of early syphilis on an ambulatory basis now can be accomplished by using the ne absorpt on del in g is c aqueous preparation which requires hospitalization One of the most recent repository preparations is crystalline procaine penicillin G in oil with 2 per cent aluminum monosterate The latter material is administered in 10 consecutive daily intramuscular injections of 600 000 units each If possible the injection should be given late in the afternoon at a time when physical activity usually can be kept at a minimum an important factor in producing a slower absorption of the penicillin

The modern use of small total doses of arsenic and bismuth concurrently with penicillin therapy has not improved the results with penicillin treatment alone It is conceivable that results with penicillin might be improved materially by increasing the amounts of arsenical and bismuth used conjointly but the latter type of therapy would defeat the basic *principle* of rapid treatment and would increase substantially the dangers inherent in arsenic and bismuth therapy It must be remembered that the use of such agents may produce an anticipated mortality rate of 1 30 000 where for practical purposes there is no danger in using penicillin alone

Even though penicillin therapy is highly effective against syphilitic infections it does not cure all patients and in order to assure more satisfactory results adequate follow up examinations are necessary During the first post treatment year the patient should be *seen at monthly intervals for physical* inspection of the skin and mucous membranes and *at each visit a quantitative* blood serologic test for syphilis should be obtained A spinal fluid examination should be done at the end of 6 months if not before At the end of one year it is advisable to give the patient a complete physical examination and to study the heart and great blood vessels by fluoroscopic examination During the second year the patient should have a physical examination and quantitative blood serologic test at intervals of 3 months and a spinal fluid examination at the end of the 24 month period During the third and later years serologic tests should be performed every 6 months for the duration of the patient s life as well as an annual physical examination

EVALUATION OF RESULTS The aim of treatment has been to secure symptomatic biologic, and serologic "cure" Symptomatic cure is not difficult to accomplish As a rule, by the end of one year, complete serologic reversal will have been achieved in 80 per cent of the patients Some 10 to 15 per cent will, at the end of that time, remain weakly seropositive with a quantitative titer of less than eight dilution units The persistence of a low serologic titer at the end of one year is not an indication for re treatment The determination of biologic cure will require years of observation in each individual patient When

of penicillin in early syphilis is usually determined by examination of the cumulative failure rates While the cumulative failure rates vary widely from clinic to clinic it is agreed generally that the composite figures indicate a failure rate for early syphilis ranging between 10 and 15 per cent There is also some indication that the failure rate is lower in patients who are treated early in the disease

CRITERIA OF TREATMENT FAILURE The cases of treatment failure can be divided roughly into two groups (1) those which show manifestations of clinical relapse in addition to increasing serologic titer and (2) those which show only a "serologic relapse" The clinical manifestations include (a) infectious relapse (b) ocular relapse (c) neurorecurrence (d) birth of a syphilitic baby, and (e) failure of the original clinical syphilitic manifestations to respond to therapy Serologic relapse can be defined as that state wherein the blood serologic test having reverted to a negative state returns to a positive state, or where the quantitative serologic titer, after falling previously, starts to show persistent rises in titer In order to make a diagnosis of a serologic relapse, repeated tests should be taken at 5 to 7 day intervals so that the changes noted above can be confirmed definitely Clinical relapses are seen frequently if serologic relapses are not treated early Reinfection syphilis may

pect since therapy for both is the same

RETREATMENT When instances of treatment failure are established unequivocally, therapy should be reinstituted The failure rate for patients requiring re treatment appears to be slightly higher than the failure rate following the first course of treatment Crystalline penicillin G in aqueous solution of a total dosage of 9 600,000 units is recommended The dosage formula should be 50,000 units every 2 or 3 hours for a total of 192 injections This will require a total of 16 or 24 days to administer Hospitalization will be required for this type of therapy For the repository form of crystalline procaine penicillin G in oil with 2 per cent aluminum monosterate, a total of 12 000 000 units will be required For a period of 20 consecutive days 600 000 units should be given daily When a second treatment failure is encountered the patient should be given the 26 week arsenic bismuth system, formerly used by the U S Army Medical Corps The following schedule will illustrate the intervals between injection of the various medicaments

TWENTY SIX WEEKS ARSENIC BISMUTH SCHEDULE FORMERLY USED BY THE U S ARMY MEDICAL CORPS

Week		
1		
2		Bismuth subsalicylate † intramuscularly once weekly, 5 doses
3		
4	Mapharsen * intravenously twice weekly total 20 injections	
5		
6		
7		
8		omit bismuth for 5 weeks
9		
10		
11		
12		Bismuth subsalicylate intramuscularly once weekly —6 doses
13	omit mapharsen 6 weeks	
14		
15		
16		

* Mapharsen dosage Adjusted approximately to body weight average dose 60 mg, minimum dose 50 mg maximum 70 mg

† Bismuth sul salicylate in oil dosage The standard dose is 0 2 gm of bismuth subsalicylate intramuscularly (not 0.2 gm of elemental bismuth metal)

TWENTY SIX WEEKS SCHEDULE (*Cont'd*)

17		
18		omit bismuth for 5 weeks
19		
20	*Mapharsen* as in	Bismuth subsalicylate intramuscularly once weekly 5 doses
21	first course twice	
22	weekly total 20 in	
23	jections	
24		
25		
26		

REACTIONS TO THERAPY Two types of reactions are encountered during the penicillin treatment of the early stage of syphilis One is the Jarisch Herxheimer reaction the other is the allergic reaction There are two types of the Jarisch Herxheimer reaction one systemic and the other local The most common systemic reaction is that of elevation of the body temperature following institution of *penicillin therapy Approximately 40 per* cent of the patients treated developed a mild febrile Jarisch Herxheimer reaction The local reaction is characterized usually by an increase in the size of inflammatory reaction of the primary or secondary lesion after initiation of therapy Neither the systemic nor local reactions are of any serious import except when the lesions are in the nose or throat, or other vital areas where an increase in the size of the lesion could cause a serious embarrassment of a vital function Adequate precaution for coping with these possibilities should be taken

Penicillin sensitivity reactions may vary from those of a slight erythema over the body including various urticarial reactions vesiculobulous *eruptions etc to those* of generalized exfoliative erythrodermias Mild sensitivity reactions may be controlled by the use of *antihistaminic therapy concurrently* with the continued use of penicillin The more severe reactions warrant however the cessation or the temporary withdrawal of therapy

Late Latent Syphilis Late latent syphilis is an infection of 4 or more years' duration in which the only finding is that of repeatedly positive serologic tests The diagnosis of this stage of syphilis is based entirely on laboratory results To establish such a diagnosis definitely the patient should have a normal physical examination normal fluoroscopic examination of the heart and grea vessels and a normal *cerebrospinal fluid* examination The possibilities of a biologi false positive reaction must be excluded Th *decision to treat cases* of previously untreated late latent syphilis is based on th desire to prevent development of late complications of syphilis The state of latency which represents an immediate equilibrium between the host and syphilitic infection implies the possibility of late complication if it remains untreated Since it is known tha about 35 per cent of untreated cases o syphilis will develop late and crippling mani festations it is felt that therapy in the latent phase is justifiable

Cases of late latent syphilis treated for a minimum of 6 months with combined arseni cal *and bismuth therapy present no indica* tions for re treatment with penicillin It has been shown that patients with latent syphilis *receiving that* amount of treatment have a 95 to 98 per cent chance of good clinical health in the future although their serologic test may remain positive in low dilution

Unlike therapy for early syphilis and the late complications of syphilis there has been no organized study of treatment results in late latent syphilis The dosage formulas now being used for late latent syphilis are the same as those used in the treatment of early syphilis For hospital use crystalline penicillin G in aqueous solution to a total dosage of 4 800 000 units is recommended The dosage schedule suggested for the aqueous solution is 50 000 units at 3 hour intervals for 96 intramuscular injections Completion of therapy will require 12 days

Therapy of late latent syphilis on an ambulatory basis is probably as effective as treatment in an institution The menstruum *recommended is crystalline procaine* penicillin G in oil with 2 per cent aluminum monostearate for a total of 6 000 000 units *This should be administered in 10 consecu*tive daily intramuscular doses of 600 000 units each

FOLLOW UP PROGRAM *The follow up pro*gram for late latent syphilis is necessarily long Since therapy is prophylactic it will require 10 to 20 years of *observation to* determine the efficacy of therapy in the individual case

It is recommended that the patient have

quantitative serologic tests and physical inspections every 3 months during the first year If the patient s progress is satisfactory quantitative blood serologic tests every 6 months and a physical examination every year are recommended thereafter It is advisable to repeat the patient s cerebrospinal fluid examination at the end of 2 years observation The yearly physical examination should include fluoroscopic examination of the heart and great blood vessels These observations should be carried on as long as the patient lives

Evaluation of Results The basic aim of treatment in late latent syphilis is prophylaxis against the development of late complications of syphilis Many years of observation will be required before any definite conclusions can be drawn concerning the efficacy of penicillin therapy in late latent syphilis

The reversal of a positive serology to negative is an unsound basis for evaluating the results of therapy It is important to remember that in infections of more than 5 years duration regardless of type of treatment a persistently positive serologic test is the rule and not the exception Such patients hereafter will be referred to as seroresistant The failure of the serologic test to revert to a negative stage is no indication that the results have been unsatisfactory regardless of the degree of improvement in the serologic titer The probability of eventual clinical progression is not greater in seroresistant patients and is indeed less in those cases whose serologic test for syphilis has reverted to a negative phase after treatment It is hoped that continued observations will make evaluation of therapy in this stage of syphilis more lucid

Criteria of Treatment Failure Treatment failure is indicated by clinical signs and laboratory findings i e the appearance of late complications of syphilis such as neurosyphilis cardiovascular syphilis visceral or benign late gummatous syphilis and/or a substantial and persistent increase in the serologic titer

Retreatment The therapy proposed for treating serologic relapse is the same as that for retreating cases of treatment failure in early syphilis doubling the total dose of penicillin and time of administration Should re treatment be required a second time the 26 week schedule formerly used by the U S Army Medical Corps is suggested

Treatment failures manifested by progression of the syphilitic infection to the late complications should receive more intensive therapy specifically recommended for the particular complication encountered

Reaction to Therapy Reactions to penicillin therapy may occur during the treatment of late latent syphilis as with other stages of syphilis Therapeutic shock the Jarisch Herxheimer reaction is encountered less frequently than in the early stages of syphilis The occurrence of a condition called therapeutic paradox is possible if a syphilitic focus has been overlooked This end stage is predicated on the assumption that therapy promotes healing so rapidly that scar formation occurs and the vital function of these scarred organs is impaired The possibility of such an occurrence in properly diagnosed late latent syphilis is extremely small Therefore under most circumstances it is recommended that the full therapeutic dose be initiated at the start of treatment If it is impossible to rule out a syphilitic infection in a vital organ it may then be advisable to start therapy with a preparatory regime in the form of smaller doses of penicillin or, in some instances to use preparatory bismuth therapy for 8 to 12 weeks before initiating penicillin therapy The occurrence of allergic reactions from penicillin therapy may be anticipated in approximately the same frequency as occurs in treatment of earlier stages of syphilis

Benign Late (Gummatous) and Visceral Syphilis This stage of syphilis may be considered as allergic in type It is characterized by the occurrence of chronic focal inflammatory lesions involving structures not essential to life or vision in syphilitic infections of 2 or more years duration The lesions involve the skin or the mucous membrane (late nodular syphilids cutaneous or mucosal gummas) the bone (periostitis osteitis osteomyelitis) or the muscles or ten[illegible] [illegible]mmas of muscles synovitis) Less the

spleen stomach lung [illegible] gummatous reactions occurring in the vital tissues such as the cardiovascular and cen

tral nervous system will be discussed later Benign late gummatous syphilitic lesions are encountered frequently in cardiovascular and central nervous system syphilis

The mode of action of penicillin in this stage of syphilis is not understood clearly The beneficial response most probably is *due to the direct treponemicidal action* of the penicillin Therapy schedules for benign late syphilis have varied widely but should be predicated on the fact that syphilis, in this stage still is a generalized disease and should be treated as such For treatment of hospitalized patients it is recommended that a total of 4 800 000 units of crystalline peni cillin G in aqueous solution scheduled in intramuscular doses of 50 000 units at 2 or 3 hour intervals for 96 injections The period of hospitalization is 8 or 12 days depending on whether the 2 or 3 hour schedule is adopted Ambulatory therapy, using reposi *tory crystalline procaine penicillin G in oil* with 2 per cent aluminum monosterate is felt to be adequate The latter material should be given in 10 consecutive daily intra muscular injections of 600 000 units each

Follow up Program The frequency of follow up visits for patients treated for be nign late gummatous syphilis should be in fluenced by the type of lesions presented Ordinarily, patients presenting gummatous lesions of the skin bones and viscera should be observed once a month and observations should be continued until clinical arrest has been secured Six to 12 months may be re quired to attain this end point Thereafter, the patient should be checked quarterly for the next 12 months with particular empha *sis on making careful physical examinations* and obtaining quantitative serologic tests A complete evaluation should be carried out after 2 years *including physical examination* fluoroscopy of the heart and great blood ves sels and cerebrospinal fluid examination If the patient s progress is satisfactory he should have a physical examination and serologic test annually for the duration of his life

Evaluation of Results Generally, peni cillin therapy for gummatous skin mucous membrane, and bone lesions yields satisfac tory clinical results Statistical results from penicillin therapy for benign late gummatous lesions, exclusive of visceral syphilis, show a treatment failure rate of 8 3 per cent The majority of treatment failures *occurred fol* lowing the use of amorphous penicillin in low total dosages Penicillin therapy as a *diagnostic aid for suspected gummatous le* sions should be used with great caution in view of the 8 3 per cent failure rate

It is agreed generally that gummatous skin and mucous membrane lesions when treated adequately with penicillin will show healing in less than 2 months There is little evidence however to indicate that the heal ing rate with penicillin therapy is any more rapid than that obtained under regimes em
[illegible]
[illegible]
[illegible]
[illegible]
late cutaneous *or mucous membrane* gum matous syphilis and it is estimated that treatment failures will occur in 5 to 10 per *cent*

The number of cases of osseous gummatous syphilis treated with penicillin is compara *tively small It has been shown that uncom* plicated periostitis osteitis, and osteomyelitis will respond satisfactorily to penicillin but cases of syphilitic osteomyelitis accompanied by sequestrum formation or extensive gum matous involvement of the adjacent skin and mucous membranes show less favorable re sults

Gummatous visceral syphilis is a relatively rare entity and often it is most difficult to make a clinical diagnosis The reports on penicillin therapy in visceral syphilis are few in number but in general they indicate satisfactory responses to the antibiotic The trend of the serologic test in patients with late gummatous stages of syphilis is not a reliable way of evaluating the efficacy of *therapy Statistical analyses reveal that most* patients with symptomatic late syphilis maintain positive serologic reactions and *that penicillin is no more effective* than other forms of syphilotherapy in producing a nega tive serologic test

In final analysis it can be stated that ap proximately 90 per cent of the cases of benign late gummatous syphilis will show *satisfactory clinical results after the adminis* tration of a single course of penicillin

Criteria of Treatment Failure. Treat ment *failure usually can be detected* by

noting the clinical response of the patient

appear A substantial increase in titer in a patient who previously had maintained a stable serologic titer is definite indication of a treatment failure

RE TREATMENT The re treatment schedules for treatment failure of benign late gummatous and visceral syphilis are the same as those recommended for early syphilis.

REACTION TO THERAPY The febrile systemic Jarisch Herxheimer reaction is encountered frequently in the therapy of this stage of syphilis and cannot be correlated with any particular type of gummatous lesion

The possibility of a therapeutic paradox
cal in
gum
volves

nonvital organs In cases of visceral syphilis the possibility of a therapeutic paradox becomes more pertinent If the signs of damage are extensive and it is felt that rapid intensive therapy could be detrimental it is suggested that therapy should consist of small initial doses of penicillin or a preparatory course of bismuth injections intramuscularly

The various allergic manifestations noted previously may occur during penicillin treatment of benign late gummatous and visceral syphilis

Cardiovascular Syphilis There is considerable controversy concerning the best type of treatment for cardiovascular syphilis and it is extremely difficult to evaluate penicillin therapy in this type of lesion In fact it is difficult to decide whether or not penicillin therapy does not cause actual harm to the patient The decision to treat such patients will of necessity be predicated on the careful evaluation of the individual case Before making a decision concerning therapy the following points should be considered Does the patient have a moderately good prognosis as to continued life? Will penicillin therapy disturb the delicate balance in the cardiovascular equilibrium of the patient under consideration?

The following facts generally support the desirability of therapy for cardiovascular syphilis Statistical studies of necropsy material have shown that in a substantial number of cases the aortas are freed of spirochetal organisms following antisyphilitic therapy In contrast in those cases that did not receive therapy spirochetal organisms could be demonstrated in their aortas An evaluation of clinical studies on syphilitic

treated cases observed over long periods of time Progression to some graver form of the disease occurred in 31 per cent of the untreated cases and only in 19 per cent of the treated cases If it is kept in mind that the purpose of penicillin therapy is to eradicate the spirochete and not to attempt the restoration of damaged tissue it appears that

that individual patient

Penicillin therapy for cardiovascular syphilis should be carried out on a hospital status A total of 6 000 000 units of crystalline penicillin G in aqueous solution is recommended The schedule of administration should be 50 000 units every 3 hours intramuscularly for 120 injections This amount of therapy will require approximately 15 days to ad

patient be started with a dosage formula of 1000 units of penicillin at 3 hour intervals intramuscularly for a period of 3 days before instituting the full therapeutic dose

Appropriate medical measures such as bed rest digitalis diuretics etc. should be used for those cases of cardiovascular syphilis in cardiac failure and antisyphilitic therapy should be withheld until the cardiac status is improved Antisyphilitic therapy for patients who have had cardiovascular failure should be approached more cautiously Whenever possible we believe a preparatory course of insoluble bismuth therapy should be given intramuscularly at weekly interval for 8 to 12 weeks before hospitaliz
pati t or penicillin treatment
he preparatory

evaluation of the patient's general medical status should be made and penicillin if warranted given in the full dosage formula

FOLLOW UP PROGRAM Patients with cardio vascular syphilis should be observed at least every 3 months for the first 2 years At each visit the patient should have a careful general physical examination with emphasis on the
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include a cerebrospinal fluid examination Provided the clinical and laboratory progress is satisfactory *semiannual observation usually* will be adequate after the second post treatment year

EVALUATION OF RESULTS No statistical re sults are available at this time because no sufficiently large series of cases has been studied The final determination of efficacy of penicillin therapy in cardiovascular syph ilis will depend on prolonged observations of larger groups of cases and an evaluation of *the results when compared with groups of* untreated control patients and groups treated with heavy metals

CRITERIA OF TREATMENT FAILURE There are no fixed clinical or laboratory criteria by which improvement in all cases of cardio vascular syphilis treated with penicillin can be measured Each individual case must be evaluated solely on its own merits An at tempt should be made to differentiate prog ression of the disease in spite of therapy from the persistence or increase in symptoms due to the residual or progressive anatomic de *fects already present* The effects of other diseases giving rise to symptoms similar to those caused by the syphilis infection should be differentiated if possible Serologic tests in this stage of syphilis are notoriously un reliable in evaluating improvement

RE TREATMENT The decision to re treat a patient will depend upon the confirmation of progression of the syphilitic infection or the appearance of manifestations of clinical or *serologic relapse* Penicillin is the drug of choice for re treatment The schedule recom mended is to double the total dose previ ously given and double the total time of ministration

REACTION TO THERAPY Since the advent of penicillin therapy, controversy has arisen *concerning significance* of therapeutic shock and the possibility of therapeutic paradox occurring in cardiovascular syphilis and treatment regimes have been altered fre quently in attempts to modify such reactions

Some feel that there has been too much emphasis placed on the significance of therapeutic shock and/or paradox It has been demonstrated that 80 per cent of the patients coming to necropsy who have had syphilis for 10 or more years will present evidence of syphilitic aortic involvement By

syphilis will show no untoward effects Furthermore it has been demonstrated by recent study that the Jarisch Herxheimer re action may not be altered even though the patient is treated over an extended period of time with preparatory small doses of peni cillin The minimal dose giving no reactions is approximately 500 units per injection Im *mediately after the individual therapeutic* dose is increased the patient may undergo a typical febrile Jarisch Herxheimer reaction Evidence indicates that reactions are as fre quent in those cases where therapy is started with small doses as with those begun with the full dosage formula

Similarly some observers feel that the so called therapeutic paradox is the natural sequence of events resulting from the damage of the syphilitic infection on vital *tissue and* is only secondarily attributable to therapy since it stops the infection and permits fi brosis to occur

All of these concepts are most interesting and important to those investigators con cerned with the problem of treating syphilis From a practical standpoint however it is suggested that each patient be evaluated in dividually If the preponderance of evidence *indicates that an edematous reaction* to treat ment or a scarred area may result from ther apy, treatment in that patient should be approached more conservatively The neces sary alterations in dosage schedule have been already pointed out

The usual allerg c reactions resulting from penicillin therapy in *syphilis also are en* countered in the treatment of cardiovascular syphilis

Syphilis in Pregnancy Over the years syphilis has proved a severe scourge to the pregnant woman desirous of a healthy infant, since the devastating action of the spirochete is greatest in the fetus The products of conception at times are damaged so severely that they are rejected from the body as a stillbirth or a miscarriage If the fetus survives, the ravages of the syphilitic infection often damage and distort the child's body and many infants have to face life severely handicapped Before penicillin, therapy was not only tedious but it did not completely insure the delivery of a noninfected infant Arsenic and bismuth therapy sometimes produced severe reactions in the mother With the advent of penicillin this situation has been altered drastically, and the outlook for both the syphilitic mother

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pregnant syphilitic patient has early syphilis

The availability of such an effective therapeutic agent for syphilitic infections in pregnancy makes it most important that every effort be made to maintain a high index of suspicion for early diagnosis It is vital that any cutaneous or mucous membrane lesions occurring during pregnancy be suspected and serologic examinations should be done repeatedly It is suggested that serologic tests be done at least every 3 months Such vigilance will help to prevent the patient from coming to term with an unrecognized syphilitic infection

For all stages of syphilis during pregnancy penicillin is the therapeutic agent of choice The concurrent use of arsenic and bismuth

suggested schedule utilizing crystalline penicillin G in aqueous solution is 50 000 units every 2 or 3 hours, intramuscularly Depending on the hours and total amount, administration will require between 8 and 15 days
Pr
cil
tio
Ingraham's work shows that repository methods using crystalline procaine penicillin G in oil with 2 per cent aluminum monosterate are equally as effective as those with the aqueous solution The total penicillin dose he recommended was 4,800,000 units This material is administered in eight consecutive daily intramuscular injections of 600,000 units each

Follow-up Program (Mothers) Follow up observation after penicillin treatment of the syphilitic mother is extremely important because of a few treatment failures After therapy and until the termination of pregnancy, monthly observations including a careful physical inspection of the skin and mucous membrane and quantitative blood serologic tests are necessary If suspicious clinical or serologic changes are observed, the patient should be seen more frequently in order to prove the possibility of treatment

tails of such follow up programs can be found under the proper section It is important to remember that a cerebrospinal fluid examination should be performed as soon after delivery as feasible

Follow up Examination (Infants) At the time of delivery a serologic test for syphilis should be made on the cord blood More important is a darkfield examination of material from the umbilical cord All infants born of syphilitic mothers should be watched for a minimum of 4 months, regardless of their serologic findings Follow up visits should be made monthly, including a careful physical examination and quantitative blood serologic tests Roentgenograms of the infant's long bones should be taken at the first and sixth week of life The necessity for treating the infant usually can be determined between the second and fourth months of life Similar observations should be carried out on the seronegative infants of syphilitic mothers It is important to remember that an infant may acquire syphilis late in gestation or become infected during delivery and thus have a negative serologic test at birth

Further comments on syphilitic infant follow up will be made under the discussion of congenital syphilis

Evaluation of Results Syphilis in pregnancy has provided the most severe test of the efficacy of penicillin therapy It is known

evaluation of the patient's general medical status should be made and penicillin if warranted given in the full dosage formula

Follow up Program Patients with cardiovascular syphilis should be observed at least every 3 months for the first 2 years At each visit the patient should have a careful general physical examination with emphasis on the cardiovascular system including fluoroscopy and a quantitative blood serologic test The evaluation after 2 years observation should include a cerebrospinal fluid examination Provided the clinical and laboratory progress is satisfactory semiannual observation usually will be adequate after the second post treatment year

Evaluation of Results No statistical results are available at this time because no sufficiently large series of cases has been studied The final determination of efficacy of penicillin therapy in cardiovascular syphilis will depend on prolonged observations of larger groups of cases and an evaluation of the results when compared with groups of untreated control patients and groups treated with heavy metals

Criteria of Treatment Failure There are no fixed clinical or laboratory criteria by which improvement in all cases of cardiovascular syphilis treated with penicillin can be measured Each individual case must be evaluated solely on its own merits An attempt should be made to differentiate progression of the disease in spite of therapy from the persistence or increase in symptoms due to the residual or progressive anatomic defects already present The effects of other diseases giving rise to symptoms similar to those caused by the syphilis infection should be differentiated if possible Serologic tests in this stage of syphilis are notoriously unreliable in evaluating improvement

Re treatment The decision to re treat a patient will depend upon the confirmation of progression of the syphilitic infection or the appearance of manifestations of clinical or serologic relapse Penicillin is the drug of choice for re-treatment The schedule recommended is to double the total dose previously given and double the total time of stration

Reaction to Therapy Since the advent of penicillin therapy controversy has arisen concerning significance of therapeutic shock and the possibility of therapeutic paradox occurring in cardiovascular syphilis and treatment regimes have been altered frequently in attempts to modify such reactions

Some feel that there has been too much emphasis placed on the significance of therapeutic shock and/or paradox It has been demonstrated that 80 per cent of the patients coming to necropsy who have had syphilis for 10 or more years will present evidence of syphilitic aortic involvement By analogy many cases with undiagnosed early syphilitic aortitis treated with the full therapeutic formula of penicillin for latent syphilis will show no untoward effects Furthermore it has been demonstrated by recent study that the Jarisch Herxheimer reaction may not be altered even though the patient is treated over an extended period of time with preparatory small doses of penicillin The minimal dose giving no reactions is approximately 500 units per injection Immediately after the individual therapeutic dose is increased the patient may undergo a typical febrile Jarisch Herxheimer reaction Evidence indicates that reactions are as frequent in those cases where therapy is started with small doses as with those begun with the full dosage formula

Similarly some observers feel that the so-called therapeutic paradox is the natural sequence of events resulting from the damage of the syphilitic infection on vital tissue and is only secondarily attributable to therapy since it stops the infection and permits fibrosis to occur

All of these concepts are most interesting and important to those investigators concerned with the problem of treating syphilis From a practical standpoint however it is suggested that each patient be evaluated individually If the preponderance of evidence indicates that an edematous reaction to treatment or a scarred area may result from therapy, treatment in that patient should be approached more conservatively The necessary alterations in dosage schedule have been already pointed out

The usual allergic reactions resulting from penicillin therapy in syphilis also are encountered in the treatment of cardiovascular syphilis

Syphilis in Pregnancy Over the years syphilis has proved a severe scourge to the pregnant woman desirous of a healthy infant since the devastating action of the spirochete is greatest in the fetus The products of conception at times are damaged so severely that they are rejected from the body as a stillbirth or a miscarriage If the fetus survives the ravages of the syphilitic infection often damage and distort the childs body and many infants have to face life severely handicapped Before penicillin therapy was not only tedious but it did not completely insure the delivery of a non infected infant Arsenic and bismuth therapy sometimes produced severe reactions in the mother With the advent of penicillin this situation has been altered drastically and the outlook for both the syphilitic mother and the fetus are greatly improved

Pregnancy may occur in any stage of a womans syphilitic infection and syphilis may be acquired at any time during the 9 month period of gestation Most often the pregnant syphilitic patient has early syphilis

The availability of such an effective therapeutic agent for syphilitic infections in pregnancy makes it most important that every effort be made to maintain a high index of suspicion for early diagnosis It is vital that any cutaneous or mucous membrane lesions occurring during pregnancy be suspected and serologic examinations should be done repeatedly It is suggested that serologic tests be done at least every 3 months Such vigilance will help to prevent the patient from coming to term with an unrecognized syphilitic infection

For all stages of syphilis during pregnancy penicillin is the therapeutic agent of choice The concurrent use of arsenic and bismuth therapy with penicillin is not recommended The total amount of penicillin should range between 4 800 000 and 6 000 000 units The suggested schedule utilizing crystalline penicillin G in aqueous solution is 50 000 units every 2 or 3 hours intramuscularly Depending on the hours and total amount administration will require between 8 and 15 days Prior to Ingrahams work on repository penicillin evidence indicated that aqueous solution of penicillin was most effective Ingrahams work shows that repository methods using crystalline procaine penicillin G in oil with 2 per cent aluminum monostearate are equally as effective as those with the aqueous solution The total penicillin dose he recommended was 4 800 000 units This material is administered in eight consecutive daily intramuscular injections of 600 000 units each

FOLLOW UP PROGRAM (MOTHERS) Follow up observation after penicillin treatment of the syphilitic mother is extremely important because of a few treatment failures After therapy and until the termination of pregnancy monthly observations including a careful physical inspection of the skin and mucous membrane and quantitative blood serologic tests are necessary If suspicious clinical or serologic changes are observed the patient should be seen more frequently in order to prove the possibility of treatment

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Further comments on syphilitic infant

nancy has provided the most severe test of the efficacy of penicillin therapy It is known

that in early untreated infectious syphilis of the mother, there is a 95 per cent risk of infection to the fetus Composite statistics show that penicillin administered in adequate doses at any time during pregnancy will assure safe delivery of 97 to 99 per cent normal living infants This remarkable and apparently paradoxical result perhaps can be explained by two factors The first factor is the ability penicillin has to permeate the placenta from the maternal to the fetal circulation in what are apparently therapeutically effective amounts, even in the very last weeks of pregnancy The second factor may merely be another indication that a syphilitic infection treated during the incubation period is much more amenable to therapy than after it has become established permanently Thus with the rapid treatment method utilizing penicillin, the fetus may be treated and in many instances cured while still in utero even though the mother acquires the infection during the latter part of the pregnancy

The results of penicillin therapy for the mother administered during pregnancy are not materially improved over the results obtained by therapy of syphilis in the nonpregnant adult

A vital question has arisen regarding the ability of a single adequate course of penicillin therapy to protect the syphilitic mother during subsequent pregnancies The consensus of nearly all observers is that women in any stage of syphilis who had previously received adequate penicillin therapy or a standard therapeutic regime with arsenic and bismuth either during a previous pregnancy or in a nonpregnant state need not be re treated during subsequent pregnancies if they continue to maintain a satisfactory clinical and serologic course This includes those women with adequately treated late latent, seroresistant syphilis It is advisable however, to follow all such women with careful observation during subsequent pregnancies. If feasible, the patient should have a careful syphilis survey, including physical examination fluoroscopy of the heart and great blood vessels, and a cerebrospinal fluid examination before each subsequent pregnancy During the pregnancy the patient should be checked at monthly intervals by careful physical inspection and quantitative serologic tests

CRITERIA OF TREATMENT FAILURE The criteria for treatment failure in syphilis in pregnancy are defined clearly As they are set up they will cover all stages of syphilis that is, primary syphilis, secondary syphilis, infectious relapse, and latent syphilis both early and late The first criterion is clinical infectious relapse or the failure of the lesions to disappear under adequate penicillin therapy The second criterion is the failure to show improvement in serologic titer whether accompanied or unaccompanied by clinical manifestations The serologic titer may fail to decline significantly during a 3 month observation The serologic relapse may be manifested by a substantial rise in a previously stationary or negative titer In pregnancy seroresistance is the rule in syphilis of 4 or more years' duration and is not an indication of treatment failure Reinfection syphilis may simulate any of the manifestations of treatment failure and for practical purposes should be managed in the same way

RE TREATMENT Cases of treatment failure in syphilis with pregnancy should be re treated according to the schedule outlined under the specific stage of syphilis concerned

REACTION TO THERAPY Therapeutic shock and the allergic manifestations are encountered in the penicillin treatment of syphilis in pregnancy in approximately the same frequency as found in the same stage of syphilis for the nonpregnant adult Observations on groups of pregnant women with syphilis treated with penicillin show that the incidence of premature births was 8 8 per cent, as compared with the premature incidence of 7 5 and 10 2 per cent for all births The consensus of opinion is that penicillin does not predispose to abortion miscarriage, or prematurity of birth even when the full dosage of penicillin is used initially

Of all the drugs administered in an attempt to prevent prenatal syphilis, it is felt that penicillin is unexcelled from all phases of observation

Infantile Congenital Syphilis This group includes syphilitic infections in the infant of 2 years of age or less The optimal time for treatment of congenital syphilis is *ante partum*, and therapy should be directed toward prevention or cure of the infection in

he fetal stage In spite of the efficacy of penicillin therapy in prenatal syphilis occasional cases of congenital syphilis may occur

The postpartum follow up program will usually make it possible to determine whether or not the infant has syphilis by the end of the third or fourth month of life and in many instances prior to that time

The clinically normal infant at the end of 6 months observation usually may be considered to have escaped infection if the serologic tests are negative It must be remembered that approximately 20 per cent of infants born of treated syphilitic mothers will still have a positive serologic test at time of birth Such noninfected infants with a positive serologic test for syphilis usually will develop a negative test by the end of 6 to 8 weeks If the infant acquires a syphilitic infection just before or during delivery the serologic test usually will be negative at birth but in all probability will become positive during the next 3 to 4 months

The treatment of choice for infantile congenital syphilis is penicillin The additional use of small amounts of arsenic and bismuth with penicillin has not added to the efficacy of therapy Penicillin is preferable because it is a safe agent and can be administered over a relatively short period of time giving an excellent over all cure rate

The total amount of penicillin to be administered is calculated on the basis of the body weight It is suggested that crystalline penicillin G in aqueous solution be used The total amount to be given is calculated on the basis of 200 000 to 400 000 units per kilogram of body weight administered intramuscularly every 2 or 3 hours The amount of each dose should be calculated in such a way that the whole course will require 8 to 15 days

No information is available concerning the efficacy of repository penicillin in the treatment of infantile congenital syphilis Until such information becomes available it is recommended that all patients with infantile congenital syphilis be hospitalized and treated with the crystalline penicillin G in aqueous solution

Follow up Program The follow up program for cases of penicillin treated congenital syphilis should be similar to that suggested for adults with early acquired syphilis Such follow up examinations will reveal early treatment failures if they exist

The follow up program should include monthly physical examination and quantitative blood serologic tests for a period of 12 months Patients with osseous congenital [illegible] have a cerebrospinal fluid examination approximately 6 months after treatment The patient should be observed every 3 months during the second year Complete evaluation should be accomplished at the end of the second year including a physical examination quantitative blood serologic test and another cerebrospinal fluid study If response to therapy is satisfactory a semiannual serologic test and an annual physical examination will be sufficient thereafter The infant should be watched for at least 5 years after therapy and longer periods of follow up may be required if the response to therapy or the stage of syphilis warrants such action

Evaluation of Results Improvement following penicillin therapy in infantile congenital syphilis is directly proportionate to the age at which the diagnosis is made and therapy instituted Comparing various penicillin treatment schedules it has been shown that satisfactory clinical and serologic results may vary between 80 and 90 per cent The clinical manifestations in congenital syphilis at all ages uniformly improve after penicillin therapy The serologic improvement becomes increasingly less prompt with the duration of the infection and shows a tendency toward stabilization of titer in older infants Statistics by Neilson and Hanchett show that serologic cures" were obtained in 100 per cent of their surviving infants treated before the age of 6 months 54 per cent of cases treated between 6 months and one year and 26 per cent of those cases whose treatment was delayed to the second year The average time for the serologic reaction to become negative in cases treated within the first 6 months of life is approximately 7 to 8 months after therapy In the majority of such cases the titers will become negative by the end of 18 months Positive spinal fluid examinations found early in the infection will tend to show definite improvement 6 to 18 months

after therapy In a similar manner congenital syphilitic infants having bone involvement will show most prompt and rapid response if they are treated in the first 3 to 6 months of the infection Of the infants born with congenital syphilis some are premature or markedly physically debilitated Despite hospitalization and excellent supportive pediatric care in addition to penicillin therapy such infants have a mortality rate of 10 to 12 per cent

Clinical relapse is relatively uncommon in infantile congenital syphilis and is estimated as less than 5 per cent Serologic relapse also is infrequent

CRITERIA OF TREATMENT FAILURE Unsatisfactory response to penicillin therapy in infantile congenital syphilis can be classified in two groups The first group includes those cases which show clinical relapse or progression The second large group consists of those cases in which results of serologic tests are unsatisfactory Platou found that clinical relapses usually occur between the third and 11th month after therapy If the serologic titer fails to decline appreciably or if there is definite indication of a rise in serologic titer a careful survey of the patient should be made in order to determine whether or not any new systems are involved

RE-TREATMENT Treatment failures in infantile congenital syphilis usually will respond to re treatment with penicillin therapy For re treatment the maximal dosage weight

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REACTION TO THERAPY It has been stated that treatment reactions can be anticipated in approximately 40 to 50 per cent of the penicillin treated cases of infantile congenital syphilis Thirty to 40 per cent develop relatively severe febrile Jarisch Herxheimer reactions The local Jarisch Herxheimer reactions occur as previously described Allergic manifestations may occur but in most instances the reactions have not been severe enough to require cessation of therapy Antiistaminic therapy is usually beneficial in ontrolling these allergic reactions due to penicillin therapy

Early in the study of penicillin treatment in infantile congenital syphilis it was felt by some that the severe systemic and local Jarisch Herxheimer reactions occurring in the debilitated or premature infant were to a large degree responsible for the 10 to 12 per cent mortality rate observed during the first 3 to 4 months of life Attempts to reduce this 10 to 12 per cent mortality rate with small doses of penicillin and excellent supportive pediatric care were unsuccessful It is probable that these patients have had their

Late Congenital Syphilis Late congenital syphilis has been defined arbitrarily as a syphilitic infection in children of 2 years of age or older Types of syphilis to be discussed are latent asymptomatic symptomatic visceral osseous and cutaneous

Penicillin therapy is effective in late congenital syphilis The total dosage formula is determined by a weight dosage ratio It is suggested that the patient be hospitalized and crystalline penicillin G in aqueous solution be used There are no results available concerning the efficacy of repository penicillin The optimal total dose is 200 000 to 400 000 units of penicillin per kilogram of body weight The total dose of penicillin should be divided and administered every 2 to 3 hours so that the total therapy will require 8 to 15 days The adult formula should be used for children over 6 years of age when the dosage weight formula calculations give a total dosage greater than 6 000 000 units

titative blood serologic test and a physical examination semiannually for 2 years and should be evaluated annually thereafter

Patients with clinical manifestations should have follow up examinations at monthly intervals until the possibility of treatment

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therapeutic results is often clouded by ana tomic damage done prior to therapy

The clinical manifestations of late con genital syphilis usually will respond readily to therapy but the rapidity with which im provement is obtained depends on the tissue involved Liver and splenic enlargement usu ally will subside slowly over an 18 month period Cutaneous gummatous lesions usually involute or definitely improve within the

measure of improvement Drop in the sero logic titer usually is slow after treatment and negative tests are attained in approximately 40 per cent of cases observed for as long as two years

Such irreparable damage may be en countered in late congenital syphilis that no amount of therapy can be effective

It appears that patients having received previous antiluetic therapy either adequate or inadequate do not respond as well to penicillin as previously untreated cases

Criteria of Treatment Failure Treat ment failure either clinical or serologic after penicillin therapy for late congenital syphilis is frequent When failure is en countered the manifestations are similar to those seen in the various stages of acquired syphilis Specifically clinical relapse progres sion or serologic relapses are found Sero logic relapse has been noted between the fourth and ninth month following treat ment The longer the duration of the syphil itic infection the more frequently are persistently positive serologic tests encount ered Persistently low titered serologic tests are not necessarily an indication of treat ment failure

The appearance of interstitial keratitis in the congenital syphilitic patient treated ac cording to the above regimen must be des ignated as a treatment failure

Re treatment Therapeutic failures in late congenital syphilis should be re treated by doubling the total dose of penicillin and the total time of administration Should peni cillin therapy fail the second time a standard heavy metal chemotherapy schedule is rec ommended

Progression of the syphilitic infection such as interstitial keratitis or neurosyphilis should receive re treatment by the schedule outlined under that specific section

Reaction to Therapy The Jarisch Herx heimer and the allergic reactions occur after penicillin therapy in late congenital syphilis The Jarisch Herxheimer reactions are en countered less frequently in late congenital syphilis The allergic reactions are as fre quent in appearance as in other stages of syphilis Management of the allergic reac tions has been previously outlined

Ocular Syphilis Syphilitic Iritis Syphi litic iritis is usually a manifestation of late secondary syphilis seldom occurring before the sixth month of infection and often as late as the second year Iritis may be associated with early infectious relapse Iritis consti tutes about 73 3 per cent of the total eye complications of early syphilis

Penicillin is a safe rapid and effective method of treating syphilitic iritis Between 4 800 000 and 6 000 000 units of crystalline penicillin G in aqueous solution are recom mended The dosage schedule recommended for aqueous solution is 50 000 units intra muscularly at intervals of 2 to 3 hours for 96 or 120 injections given in 8 to 15 days

The use of repository penicillin on an ambulatory basis will probably be as effec tive as the use of aqueous solution Crystal line procaine penicillin G in oil with 2 per cent aluminum monosterate is one of the most recent preparations This latter material is given in 10 daily intramuscular injections of 600 000 units each

Ocular syphilis should be treated con

syphilitic iritis should be the same as that outlined in the section on early syphilis

For the first treatment failure it is sug gested that penicillin be used doubling the total dose and the total time of administra tion The therapy suggested for a second treatment failure is the 26 week heavy metal therapy program formerly used by the Medi cal Corps of the U S Army

Syphilitic iritis uniformly responds well to penicillin therapy Beneficial effects usually are noted by the second day of treatment and in most cases complete improvement will occur by the 21st day In nearly all pa tients the visual acuity will return to normal

or to that prior to infection Prolonged infections without concurrent ophthalmologic care frequently will result in permanent visual damage

Treatment failure may be both clinical and serologic The iris may show recurrence of the inflammatory process Infectious relapse such as mucocutaneous and neurologic is encountered and usually will show a prodromal increase in the serologic titer Similarly serologic relapse may occur alone

Reactions to penicillin therapy for syphilitic iritis are the same as those seen in other stages of early syphilis A local Jarisch Herxheimer reaction may be manifested by an aggravation of the ocular inflammation This local reaction will usually occur during the first day of treatment Symptoms of photophobia lacrimation and pain may occur or increase in the inflammatory process and may be demonstrable by use of the corneal microscope and slit lamp

The allergic reactions to penicillin therapy in syphilitic iritis are those commonly encountered in early syphilis

Interstitial Keratitis Interstitial keratitis is a common occurrence in congenital syphilis It has been shown that 52 per cent of all persons brought to medical attention because of congenital syphilis have interstitial keratitis Interstitial keratitis is rare in secondary syphilis and even after chancres of the eyelid

The cause of interstitial keratitis is unknown It is conjectured but not proved that the lesion is in some way due to infection allergy Interstitial keratitis is seen most frequently between the ages of 5 and 16 years Patients who are untreated or poorly treated will have residual damage to the vision in an estimated 20 to 40 per cent The process produces an inflammation of the entire cornea with grayish infiltrates toward the periphery and subsequent vascularization Severe photophobia lacrimation and conjunctivitis are the symptoms presented

Treatment of interstitial keratitis has produced highly variable and unpredictable results Penicillin therapy alone for interstitial keratitis has been discouraging It is the gen

pitalized and carefully studied for his ability to tolerate hyperpyrexia

Six million units of crystalline penicillin G in aqueous solution are recommended The dosage schedule suggested is 50 000 units intramuscularly at 2 or 3 hour intervals for 120 injections The first schedule will require 12 days and the second 15 days Hyperpyrexia should be used concurrently with the penicillin therapy A temperature above 39 2° C should be maintained for a minimum of 25 hours For information concerning the type and method of producing artificial hyperpyrexia the reader is referred to standard textbooks on this subject

Ambulatory repository penicillin therapy is not recommended in the treatment of interstitial keratitis

Concurrently with systemic therapy favorable results have been reported using penicillin locally in patients with interstitial keratitis Penicillin was introduced by iontophoresis cotton pad soaks and ophthalmic ointment

Klauder s report indicates that the active interstitial keratitis is not altered specifically by penicillin therapy It has been shown repeatedly that penicillin therapy does not prevent the initial attack of interstitial keratitis nor will it prevent involvement of the second eye or recurrence in the previously afflicted eye Klauder believes fever therapy is still the treatment of choice Even though penicillin has no advantage over chemotherapy as to results it is probably the best adjunct treatment for fever

Therapy for interstitial keratitis is still far from satisfactory

The follow up studies for patients with interstitial keratitis are the same as those outlined for the appropriate stage of the accompanying general syphilitic infection In addition to the usual studies careful ophthalmologic examinations should be made at each visit including visual acuity wi [illegible]

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most common manifestation of treatment failure Treatment failure or progression is seen frequently after penicillin therapy alone The serologic reaction in interstitial keratitis is not a reliable means of evaluating treatment failure It is possible that serologic

relapse will occur after treatment of interstitial keratitis and may be the prodromal

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bined penicillin and fever therapy The penicillin dosage and time of administration should be doubled Twenty five hours of fever therapy by an accepted method should be used For a second treatment failure the 26 week heavy metal therapy program as previously used by the U S Army Medical Corps combined with fever therapy is recommended Fever therapy above the level of 39 2° C at this time should be given in the full therapeutic dose of 40 to 50 hours

Jarisch Herxheimer reactions are encountered frequently in penicillin therapy for interstitial keratitis There have been no indications that penicillin therapy will produce a local Jarisch Herxheimer reaction involving the cornea

Allergic manifestations resulting from penicillin therapy also occur during the penicillin treatment of interstitial keratitis

Syphilitic Primary Optic Atrophy Syphilitic primary optic atrophy is a syndrome characterized by gradually diminishing vision and almost always associated with tabes dorsalis taboparesis or general paresis The syphilitic infection or its toxic products apparently slowly destroy or render nonfunctioning the fibers of the optic nerve The peripheral portions of the visual fields usually are destroyed first Earliest diagnostic aids in this syndrome are the occurrence of simple scotomata and a diminution of the visual fields It is believed that considerable permanent damage will have been done when the clinical symptoms become evident Early diagnosis and treatment are paramount in preventing loss of vision

It appears that combined penicillin and fever therapy is the treatment of choice Hospitalization is recommended The patient s ability to tolerate hyperpyrexia should be studied A total dosage of between 6 000 000 and 8 000 000 units of aqueous crystalline penicillin G is recommended The administration schedule suggested is 50 000 units intramuscularly every 2 or 3 hours for 120 to 160 injections The complete administration will require between 12 and 20 days Hyperpyrexia should be induced concurrently with the penicillin therapy A minimum of 25 hours of fever above 39 2° C is felt to be adequate for most patients

Repository penicillin therapy on an ambulatory status is not considered adequate treatment

Follow up studies on patients with syphilitic primary optic atrophy should be the same as those outlined for the accompanying stage of neurosyphilis In those rare instances where the cerebrospinal fluid is not involved the follow up studies should be the same as those outlined for tabes dorsalis including visual acuity and visual field examinations

The evaluation of any form of therapy for primary optic atrophy is obscured by the frequent occurrence of progressive blindness in spite of assumed adequate therapy and laboratory evidence of an arrested general syphilitic infection The duration of the infection before institution of treatment appears to be an important factor in the ultimate outcome There is a wide divergence of opinion among observers concerning the effectiveness of therapy in the

to be the optimal therapeutic regimen now available

Therapeutic results in primary optic atrophy are extremely difficult to evaluate with the present known methods It is almost impossible to determine whether the progression of clinical symptoms and signs is due to continued activity of the syphilitic process or due to the fibrosis accompanying healing Study of the spinal fluid will help determine the over all effectiveness of therapy of central nerv

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of visual acuity and visual fields are only moderately helpful

Failure of the cerebrospinal fluid to improve after therapy is an indication for retreatment as with other stages of neurosyphilis

Evaluation of treatment results must be done on the individual patient basis using all the clinical and laboratory information available

If treatment failure is based on the failure of the cerebrospinal fluid to improve or if it shows reactivation, therapy appropriate for that stage of neurosyphilis is suggested

If the patient becomes progressively blinder during a 6 month period after treatment, it is suggested that treatment be re introduced using the original formula of 6,000 000 to 8 000,000 units of penicillin and fever therapy above 39 2° C for 25 hours This is to be administered regardless of the titers obtained or examinations of the cerebrospinal fluid or blood

The febrile Jarisch Herxheimer reaction has been reported in penicillin treatment of primary optic atrophy Such reactions occur less frequently than in early syphilis

Neurosyphilis Syphilis of the nervous system produces a variety of clinical and pathologic entities A classification can be made on the basis of the tissue involved and the pathologic responses The meninges, blood vessels, or parenchyma of the brain usually are attacked The pathologic reaction may be either inflammatory or degenerative in type Clinical syndromes have been de scribed because the syphilitic infection re produces the same reactions in many patients All stages of these syndromes are encountered and will mirror the activity of the syphilitic infection or the resultant damage

The changes in the cytologic and chemical components of the cerebrospinal fluid are more reliable than the clinical manifesta tions for indicating the activity of the syphilitic infection in the neural tissues

Clinically the various syndromes are designated as follows

(1) Asymptomatic nervous system syphilis
(2) Diffuse meningovascular syphilis
(3) Acute syphilitic meningitis
(4) General paresis
(5) Tabes dorsalis
(6) Taboparesis
(7) Vascular neurosyphilis including thromboses and hemorrhage of the cerebral and spinal vessels
(8) Gumma of the brain and spinal cord
(9) Syphilitic epilepsy (nonparetic)
(10) Erb's spinal spastic paraplegia
(11) Nerve deafness

Spinal Fluid Examination Since the days of Wagner-Jauregg the effects of anti syphilitic therapy have been measured by alterations produced in the cerebrospinal fluid findings, as well as clinical improvement Study of the changes in the cerebrospinal fluid components is an objective method of evaluation The proper evaluation of a cerebrospinal fluid requires (1) a cell count performed immediately after being drawn, (2) quantitative total protein deter mination, (3) specific quantitative complement fixation test for syphilis, (4) a colloidal protein test either gold or mastic *

The cell count affords the most valuable information as to the immediate activity of the syphilitic infection in the nervous sys tem A count of more than 5 cells per cubic millimeter is considered evidence of activity An increase in the total protein determination also indicates activity of the infection or degenerative reaction in the nervous system tissue The colloidal test utilizing the globu lin fraction to a lesser degree indicates activity and tissue destruction These latter two tests do not change as rapidly as the cell count The complement fixation reaction for syphilis determines the specificity of the process The serologic reaction usually is slow to develop and disappears equally as slowly

For complete evaluation of neurosyphilis and its therapy both clinical and laboratory tests must be utilized in individual cases

There appears to be general agreement that penicillin is the drug of choice in neuro syphilitic therapy and has replaced metal chemotherapy Differences of opinion exist concerning the efficacy of penicillin therapy alone as against combined penicillin and fever therapy The additional benefit of fever therapy in combination with penicillin is predicated on two facts (1) It is well known that fever therapy has definite clinical value in the treatment of neurosyphilis, (2) it has been shown experimentally that the spiro-

* We feel that the colloidal protein test is of little value in diagnostic and therapeutic evaluation of syphilis of the central nervous system However since it is in common use we will indicate the effects of therapy on this test

chetıcıdal actıvıty of penıcıllın ıs enhanced ın the presence of temperature elevatıons Clınıcal studıes by Dattner show that the

and his associates have found after long term observations that penıcıllın therapy alone ıs as effectıve as combınatıon therapy

Sıx mıllıon to 10 000 000 unıts of penıcıllın are recommended for the treatment of asymptomatıc, acute menıngeal, dıffuse menıngovascular, gumma, and vascular neurosyphılıs Utılızıng hospıtal care, aqueous crystallıne penıcıllın G gıven ın a dosage schedule of 50,000 unıts ıntramuscularly every 3 hours over a perıod of 15 to 25 days ıs recommended Unpublıshed ınformatıon ındıcates that reposıtory penıcıllın may be equally as effectıve as aqueous crystallıne penıcıllın G A recent preparatıon ıs crystallıne procaıne penıcıllın G ın oıl wıth 2 per cent alumınum monosterate The ambulatory schedule should be daıly ıntramuscular ınjectıons of 600,000 unıts each for 10 to 17 days

For the degeneratıve types of neurosyphılıs, such as paresıs tabes dorsalıs, and taboparesıs, 8 000,000 to 12 000,000 unıts of penıcıllın are recommended The patıent should be hospıtalızed and gıven 50 000 unıts of aqueous crystallıne penıcıllın G, ıntramuscularly every 3 hours for a perıod of 20 to 30 days

Ambulatory reposıtory penıcıllın therapy ıs not recommended as the treatment of choıce for degeneratıve stages of neurosyphılıs

In ındıvıdual patıents whereın the clınıcal manıfestatıons warrant and the physıcal condıtıon wıll permıt, fever therapy can be utılızed It ıs suggested that hyperpyrexıa be ınduced by the standard method, maıntaınıng the fever above 39 2° C for a mınımum of 25 hours but preferably 50 hours The decısıon to use fever therapy should rest upon the merıts of the ındıvıdual case

Follow up Program The followıng standard program ıs suggested as a basıs for evaluatıng penıcıllın treated neurosyphılıtıc patıents The fırst year after treatment observatıons should be made every 3 months Semıannual examınatıons should be made thereafter for the next 4 years After 5 years annual evaluatıons wıll be adequate ıf the patıent's progress ıs satısfactory Lıfetıme observatıon ıs advısable These follow up observatıons should ınclude an ınterval note, physıcal examınatıon, quantıtatıve blood serologıc test, and a cerebrospınal fluıd examınatıon Each cerebrospınal fluıd sample should be subjected to a cell count, quantıtatıve total proteın determınatıon, colloıdal proteın test (gold or mastıc), and a complement fıxatıon test Specıal emphasıs should be placed on examınatıon of the patıent's mental status and nervous system, by a psychıatrıst ıf possıble

Evaluation of Results To evaluate properly the effıcacy of penıcıllın therapy ın neurosyphılıs both the clınıcal and laboratory fındıngs must be consıdered The clınıcal fındıngs are more dıffıcult to ınterpret sınce some of the symptoms and sıgns may be due to permanently damaged or destroyed tıssue

Changes ın the cerebrospınal fluıd components are an objectıve method of studyıng actıvıty of the syphılıtıc ınfectıon The Dattner Thomas concept of spınal fluıd actıvıty ıs the presently accepted standard of measurement Brıefly thıs concept states that ıf therapy has been successful there wıll be a progressıve reductıon ın the cerebrospınal fluıd cell count and proteın content toward normal Over a longer perıod the colloıdal proteın test (gold or mastıc) and the spınal fluıd complement fıxatıon test for syphılıs wıll revert to negatıve The cerebrospınal fluıd may be rendered ınactıve, unassocıated wıth defınıte clınıcal ımprovement The clınıcal evaluatıon of response to penıcıllın therapy ın the neurosyphılıtıc patıent ıs more dıffıcult In order to provıde a basıs of comparıson, pre and post penıcıllın therapy, all symptoms and sıgns need to be studıed objectıvely A careful hıstory and physıcal ex

spınal cord, or perıpheral nerves

According to Moore, results of penıcıllın-

paresis—increased cell counts in the spinal fluid promptly become normal sometimes within a few days even during the period of treatment but practically always within 60 days The elevated protein content in the cerebrospinal fluid likewise becomes normal in a period of 2 to 3 months Colloidal protein (mastic or gold) curves tend to become normal as the proteins fall to normal The positive cerebrospinal fluid complement fixation test in a like manner progresses toward normal The rate at which the complement fixation test becomes normal depends upon two factors (1) the duration of infection in the patient and (2) the degree of positivity i e the titer of the cerebrospinal fluid before treatment is given He also found that the over all beneficial effects on the cerebrospinal fluid were approximately 90 per cent regardless of the type of neurosyphilis There was evidence of cerebrospinal fluid relapse in only 10 per cent of the patients

Because of the diversity of clinical response and the variation in criteria established by different observers no statistics on clinical improvement will be presented The *clinical response of neurosyphilis to penicillin* has varied from complete relief of symptoms to progression and death in spite of therapy

Evaluation of Results of Specific Types of Neurosyphilis *Asymptomatic* The evaluation of penicillin therapy in cases of asymptomatic neurosyphilis is based entirely on laboratory findings Penicillin therapy for asymptomatic neurosyphilis is felt to be effective Few if any cases under therapy *show signs* of progression and the cerebrospinal fluid abnormalities return to normal following therapy The cell count is reduced to a striking degree and usually returns to normal within 10 to 24 weeks The cerebrospinal fluid proteins generally revert to a normal level in approximately 6 months and remain there The complement fixation titers

fection

Serologic tests respond in a manner similar to those in patients with early or late syphilitic infections not involving the spinal fluid

Diffuse Meningovascular Syphilis Meningovascular neurosyphilis and asymptomatic neurosyphilis respond similarly to penicillin therapy at least from a laboratory standpoint The clinical improvement in meningovascular syphilis usually is good but will depend upon the amount of permanent damage

Acute Syphilitic Meningitis Penicillin therapy for acute syphilitic meningitis has produced excellent results with prompt symptomatic improvement The symptoms of headache stiff neck and cranial nerve paralysis quickly disappear and there is gradual improvement of nerve deafness and relief of convulsions Serologic and cerebrospinal fluid findings revert to and remain normal

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paresis or taboparesis Studies of groups of investigators under the sponsorship of the National Institute of Health show that mental improvement can be expected in about 50 per cent of the patients with paresis but *in 20 to 40 per cent there is no improvement* or deterioration and in 6 to 10 per cent death occurred within 2 years after treatment Stokes and his associates showed that the results arising after malaria therapy appeared superior to the penicillin results after the first or second year of observations but were equalled using penicillin therapy after the third year Improvement in the cerebrospinal fluid abnormalities is superior with penicillin therapy Many instances of improvement in speech and writing defects tremor and other neuropsychiatric symptoms are seen

Tabes Dorsalis The efficacy of penicillin therapy in tabes dorsalis has been definitely proved Stokes and his associates *indicate* that 80 per cent of the patients with tabes dorsalis having Type III spinal fluids (marked increase in cell count and total protein) achieved marked improvement after *the third year The improvement* in cerebrospinal fluid abnormalities after the second year is twice as good with penicillin as with malaria therapy Solomon states that penicillin therapy is highly effective in bringing the cerebrospinal fluid to normal He feels

that early diagnosis and treatment of patients with tabes dorsalis will produce the best symptomatic results

Taboparesis The studies of Stokes and his associates *show that 60 per cent of cases in* their series of taboparesis had marked improvement in the cerebrospinal fluid abnormalities at the end of 3 years They feel that *cerebrospinal fluid improvement is superior* with penicillin alone and that symptomatic improvement is equal to malaria therapy after the second year

Syphilitic Epilepsy (Nonparetic) Peni [illegible] on [illegible] llin therapy produces no clinical and only moderate cerebrospinal fluid improvement Few cases of Erb s spinal paraplegia treated with penicillin have been reported

Nerve Deafness Cranial nerve palsies occurring in early meningeal syphilis usually [illegible]

Impairment in hearing however has been arrested in other patients

Criteria of Treatment Failure Treatment failure in neurosyphilis is manifested either by progression of clinical or laboratory findings or as is most common both It is [illegible] gression in spite of normal or improving cerebrospinal fluid findings

Careful serial study of the cerebrospinal fluid findings either will confirm a clinical treatment failure or predict its potential occurrence

Using the Dattner Thomas concept of *cerebrospinal fluid activity most of the failures will show an initial increase in cell* count and quantity of total protein present Later the colloidal protein (mastic or gold) test and the complement fixation test will become more positive

[illegible]

Re treatment When the initial course of penicillin fails in patients with asymptomatic *neurosyphilis*, acute syphilitic meningitis and meningovascular syphilis it is recommended that the total dose of penicillin and the duration of therapy be doubled

When the degenerative types of neurosyphilis fail to respond to the initial treatment it is recommended that the total penicillin dose and interval of administration be doubled in addition to receiving a full 50 hour course of hyperpyrexia concurrently

Reaction to Therapy Penicillin treatment reactions are found in all stages of neurosyphilis About 25 per cent of all patients with neurosyphilis treated by penicillin will show a mild febrile Jarisch Herxheimer reaction Local Jarisch Herxheimer reactions characterized by an increase in symptoms frequently are seen A series of patients with general paresis treated by Callaway and his associates showed increase in symptoms in approximately one third of the cases Moore believes that therapeutic shock is an all or none phenomenon and therefore advocates administration of full therapeutic doses of penicillin unless specific contraindications exist in the individual case

[illegible] ha [illegible] ne [illegible] and with the same frequency Suggested management is the same as that under early syphilis

Miscellaneous Problems Associated with the Treatment of Syphilis Oral Penicillin The oral penicillin treatment of syphilis is mentioned only to be condemned Oral penicillin preparations although improved still require large doses and prolonged administration for syphilotherapy This immediately places the control of administration in the patient s hand Self therapy of syphilis is felt to be too precarious to recommend it for large scale use

The Effect of Penicillin Therapy for *Other Purposes as a Source of Confusion* in Management of Syphilis Penicillin is used for innumerable purposes at present so that the unrecognized syphilitic patient may be given varying amounts of *penicillin for* other diseases before the syphilitic infection is discovered Such a situation will obviously confuse the evaluation of the patient s syphilitic infection.

Penicillin therapy for gonococcal urethritis and cervicitis is one of the most important sources of such confusion Various possibilities will be outlined It is conceivable that the therapeutic penicillin dose used for the gonococcal urethritis could cure completely a coincidental syphilitic infection *On the other* hand the incubation period of the primary lesion may be delayed or it may permit an asymptomatic infection to develop Generally the amount of penicillin for the urethritis should be considered as inadequate for a syphilitic infection and each patient should be followed carefully to eliminate syphilitic relapse manifestations

It is recommended that all patients with gonococcal urethritis or cervicitis be followed clinically and serologically for 4 to 6 *months after their penicillin therapy* The patient should be seen bimonthly for 2 months and monthly thereafter to have a physical inspection and a serologic test

When penicillin therapy is started or completed before the positive serologic test is discovered the following procedure is suggested Immediate arrangements for a complete syphilitic evaluation should be made This examination should include a careful history physical examination quantitative blood serologic test a cerebrospinal fluid *examination and fluoroscopy* of the heart and great blood vessels The accumulated information often will result in clarifying the situation On the basis of the diagnosis the need for further therapy can be decided The initially administered penicillin may be adequate or a complete course of penicillin may need to be instituted Appropriate follow up studies should be made after therapy to insure favorable results

Caution in making a diagnosis of syphilis is urged since other conditions which respond *to penicillin may produce* a biologic false positive reaction

One Day Abortive Therapy for Sexual Contacts of Patients with Early Syphilis Alexander and Schoch for several years after the advent of penicillin therapy treated contacts of patients with proved early syphilis with one day abortive antisyphilitic therapy Their results show that of 130 untreated sexually exposed patients 76 developed clinical syphilis as compared with 115 sexually exposed abortively treated patients of whom only 6 developed syphilis at a later date Second contacts with infected persons could not be excluded in the 6 failures This abortive therapy has potentialities in the prophylaxis against syphilis but further long term follow up studies are required to confirm its effectiveness This program is still in the investigational stage and its general use is not encouraged

New Antisyphilitic Agents Recent preliminary reports indicate that aureomycin *(duomycin) is effective against Treponema pallidum* infections in man The material is administered orally and appears to alter the syphilitic infection much as penicillin does Further investigation will be required before more definite statements can be made about its effectiveness

Prevention or Control of Syphilis The dream that a rapid method of treating syphilis would eradicate it from society has not been realized with penicillin therapy Control of syphilis still depends on the epidemiologic follow up on contacts and potential sources of infection as well as treatment The foundation of such a combination of effort is the private physician or practitioner for to be effective each physician must obtain as much information from each venereally infected patient as possible concerning his source of infection or other possible contacts From such information he can get the potentially infected patients under his observation or turn the information over to his local health department for further action The failure to discover and treat infections among contacts leaves an unchecked source of in

health department is essential if the community and ultimately the country are to *control syphilis.*

J LAMAR CALLAWAY
ARTHUR H FLOWER JR.

TROPICAL TREPONEMATOSES
(Yaws)

Yaws is an infectious nonvenereal contagious disorder caused by the *Treponema pertenue* which exists endemically in certain tropical countries and occurs primarily in children and adults of the dark skinned races

Clinically the disease appears in three rather distinct stages The primary lesions usually are solely cutaneous The secondary lesions involve the skin and often have associated systemic symptoms The late or tertiary stage is characterized by gumma formation in the skin and bones Lymph node involvement is a common occurrence in yaws

It has long been known that yaws will re

of syphilis it was suspected that penicillin would be effective against yaws and it was proved by the studies of Dwinelle Sheldon Rein and Sternberg A dosage of 1 200 000 units of crystalline procaine penicillin G given on an ambulatory basis appears adequate Two intramuscular injections of 600 000 units each on alternate days are apparently as effective as therapy every 3 hours for 4 days The repository form of crystalline penicillin G in oil with 2 per cent aluminum monosterate is the most effective recent product Patients between 6 and 12 years of age are given 600 000 units those between 13 and 16 years of age are given 900 000 units as a total dose All patients above 17 years of age are given 1 200 000 units of penicillin

Evaluation of Results General observations show that the primary and secondary lesions of yaws respond rapidly and uniformly to penicillin therapy Most of the lesions disappear within the first week The late clinical manifestations of yaws improve more slowly

Serologic response to treatment however is quite different Out of a large group of 466 patients only 16 6 per cent of the entire group became seronegative at the end of 12 months observation If those who showed clinical improvement plus marked diminution in the serologic test are added to the seronegative group approximately 90 per cent can be considered to have had a satisfactory result Increasing the total amount of penicillin does not appear to improve the serologic results although there are some indications that some improvement may be obtained by prolonging the period of treatment The above conclusions are drawn from patients treated with repository penicillin in beeswax and oil

Criteria of Treatment Failure Treatment failure in penicillin therapy for yaws usually will appear as clinical and/or serologic relapse New lesions may appear and/or the serologic test may show increase in titer if treatment was not effective Reinfection is an ever present possibility since the infection is disseminated so widely The clinical differentiation of relapse from reinfection is sometimes impossible but for practical management all such cases should be considered as treatment failures

Re treatment Treatment failures should be re treated by doubling the total penicillin dose and total duration of therapy

Reaction to Therapy In the cases studied no severe reactions were encountered Approximately one half of the treated patients showed an elevation of temperature 2 to 8 hours after institution of therapy Secondary elevations of fever were noted on the third fourth and fifth days in approximately one fifth of the patients treated These reactions can be considered as systemic Jarisch Herxheimer reactions

Allergic reactions following penicillin therapy in yaws were not reported in the series studied

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PINTA

This is a nonvenereal disease endemic in the tropical regions of the Western Hemisphere produced by the *Treponema carateum* and occurs most frequently among the dark skinned races

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ports show that 1 200 000 units of repository crystalline procaine penicillin G in oil with 2 per cent aluminum monosterate is effective Several schedules of administration were used The method using a single injection technic appeared to give satisfactory results More prolonged schedules of administration are under study

The evaluation of the clinical improvement and the serologic response must await further observations

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BEJEL

Bejel is a nonvenereal treponemal infection occurring only among Bedouins of the Euphrates Valley The disease occurs primarily in childhood The spread of the disease is by personal contact from child to child or child to adult Certain fomites such as utensils and other objects may be incriminated in the transmission of bejel Early clinical lesions usually are desquamating grayish nonulcerating patches on the oral mucous membranes The most common late lesions are ulcerations of the nasopharynx nodular lesions of periarticular areas and hyperkeratotic lesions on the soles of the feet Painful osseous gummatous lesions have been observed Visceral manifestations of bejel are unknown

The complement fixation and flocculation tests for syphilis are almost always positive in bejel particularly in the late stages Bejel is apparently not passed from mother to *fetus in utero*

The lesions of bejel will respond to heavy metal syphilitic therapy By analogy it is assumed that penicillin will be an effective therapeutic measure The total dose of penicillin and the formula of administration used for the other tropical treponematoses will probably be effective

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AMEBIASIS

Any concept of the therapeutic approach to the treatment of amebiasis involves serious consideration of the incidence of the disease in a temperate zone climate such as the United States fundamental differences in the nature of the disease in the temperate zone as compared with the tropics and the extent of tissue invasion and means of ascertaining the same before any principles of treatment can be outlined It is of historical interest that the Chicago amebiasis epidemic of 1933 was the first instance of the disease having assumed epidemic proportions in a temperate zone area Epidemic amebic dysentery did occur in British troops stationed in Egypt Macedonia and Palestine during World War I but the circumstances were considerably different from those resulting in the widespread infection of a civilian population as occurred in Chicago

Subsequent to the Chicago epidemic Spector studied 10 108 patients in the Chicago area between the years 1933 and 1937 Of this group 4 478 persons were without complaints Of the total group surveyed 3 4 per cent were found to be infected Roda

niche and Palmer continued these surveys made at the University of Chicago Clinics and from 1938 to 1941 studied 2 691 patients reporting an incidence of 1 8 per cent From 1943 to 1946 Palmer and Prescott studied 1 132 patients again at the University of Chicago Clinics with a reported incidence of 1 4 per cent During the same time interval covered by the last Palmer report Dolkart and Hedges studied 3 605 patients at St Lukes Hospital Chicago Of this group 1 070 patients had gastro intestinal complaints as their presenting symptoms and 3 5 per cent had stools positive for *E histolytica* An over all incidence of 1 5 per cent was encountered

Craig and Faust have tabulated the results of surveys made on population samples in different parts of the country These results indicate an average incidence of amebiasis ranging from 5 to 10 per cent Some groups of investigators have claimed incidences as high as 25 per cent of the adult population infected with *E histolytica*

In studies at the United States Naval Medical Center Michael gave some clue as to the role of returned service personnel from World War II in creating increased spread of amebiasis It was concluded that intestinal parasites were not introduced in sufficient numbers to contribute to any public health hazard Of 1 000 Naval returnees from endemic amebiasis areas 8 9 per cent had positive stool identifications for *E histolytica* Of 1 000 repatriated prisoners of war from similar areas 3 1 per cent had positive stools for *E histolytica*

Because of the difficulties involved in proper identification of *E histolytica* the different incidences reported throughout the country can be explained by the different criteria used in the various laboratories for
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much less rigid diagnostic criteria It is extremely difficult to distinguish between the trophozoite stage of *E histolytica E nana* and *E coli* and unless the organism is recovered from the wall of an abscess or from a mucous membrane lesion we believe that the organisms must be grown in culture before a positive identification can be made This opinion was expressed by Dr C W Rees of the National Institute of Health who collaborated with us in the initial setting up of our laboratory and procedures at St Lukes Hospital

These aspects of diagnosis are discussed because the dangers inherent in treating an individual for amebiasis on the basis of an incorrect diagnosis are fully as serious as missing the diagnosis by inept laboratory identification We share with Dr Rees and others the opinion that *E histolytica* can at times be a luminal parasite the so called carrier state without producing active tissue invasion Stopping diagnostic procedures upon the identification of *E histolytica* in the stools of patients with gastro intestinal symptoms in the carcinoma bearing age group cannot be countenanced Negative roentgenographic studies of the gastro intestinal tract and sigmoidoscopic examination must be carried out before amebacidal therapy is initiated

Some knowledge of the growth characteristics of *E histolytica* is essential to a knowledge of a means of growth prevention It is well known that one of the great obstacles in research studies of the organism is that it cannot be grown in pure culture but rather requires the symbiotic activity of other organisms Rees by careful technic has been able to grow *E histolytica* with only one contaminating organism for symbiotic activity and consequently it was possible for him to develop for the first time an antigen of sufficient sensitivity to make possible a reasonably accurate complement fixation test as an aid in the diagnosis of amebiasis *if tissue invasion is present* More than 20 years ago Hegner reported a series of observations during which he studied the protozoan content of the stools of various animals in the Baltimore Zoo It was observed that the carnivores had no protozoa in their stools omnivores had a moderate number and the herbivorous animals had stools loaded with all varieties of protozoa He suggested at that time that a high protein low carbohydrate diet might be of value in the treatment of amebiasis in humans Apparently the carrying out of this suggestion has not become a matter of record because no such reports have been encountered We have studied several patients

particularly some refractory to all forms of amebacidal therapy, and have found that negative stool cultures may be promptly obtained by such a procedure associated with which there was an amelioration of symptoms It would seem reasonable that the mode of action of a high protein low carbohydrate diet is to alter the bacterial flora of the intestinal tract in such a way as to make further growth of the amebae difficult by virtue of altering the necessary symbiotic activity of other organisms These observations are in agreement with the changing concepts of bacterial growth, so excellently demonstrated in the work of Dubos and of Waksman, in which there is less concern with the growth rate of an organism in a culture tube than with the growth rate of the organism in its normal environment where the nutritional effect of serum, exudate, and/or the enzyme systems of other bacteria in the environment are at work

There is good pharmacologic evidence that the action of the various amebacidal drugs in the test tube is not comparable to their action in vivo Perhaps some of the amebacidal activity is due to alteration of the bacterial flora of the digestive tract, making amebic growth impossible, rather than there being a direct effect exerted on the amebae themselves

Specific Therapy. IODOXYQUINOLINE COMPOUNDS These are mentioned first because they are the least toxic and have the widest range of usefulness

Diodoquin This is available in 0 2 gm tablets containing 63 9 per cent of iodine The daily dosage is from 1 8 to 2 0 gm for 20 days Repeated courses may be employed freely but as with the other amebacidal drugs adequate recheck stool examinations should be carried out In chronic refractory cases, 0 6 to 1 2 gm of the drug may be given daily for periods of several weeks There is some justification for the use of this drug as a prophylactic for individuals who are making trips into known endemic amebic dysentery areas Two individuals in such a situation in Mexico, were maintained by the author on 0 6 gm daily for a period of 2 years without harmful effect Untoward reactions may occur in iodine-sensitive individuals, despite the fact that relatively little if any iodine absorption is supposed to take place from the bowel On occasion constipation or pruritis may occur following the administration of diodoquin or any of the other

because of the insolubility of the iodine

Vioform This is supplied in 0 25 gm tablets or capsules containing 41 per cent of iodine The daily dosage is 0 75 gm per day for 7 to 10 days It has been suggested that courses be repeated if necessary after a 7 day interval of rest There would seem to be little reason not to employ this drug in larger dosage, especially in view of the lower iodine content Apparently 0 75 gm per day was the dosage first recommended and custom has decreed its continuance

Chiniofon Chiniofon (sodium iodoxyquinoline sulfonic acid containing 26 to 28 per cent iodine) was first introduced by Muhlens and Menk in 1921 and was marketed under the proprietary name of "yatren" It is also marketed under the name of "anayodin" The dosage is the same as for vioform, namely, 0 75 gm daily for 7 to 10 day intervals It is supplied in 0 25 gm tablets It would appear that the lower iodine content makes chiniofon less desirable than either vioform or diodoquin as a choice in therapy

ARSENICALS *Carbasone* Carbasone is available in 0 25 gm capsules, dosage recommended is usually 0 50 to 0 75 gm daily for 7 to 10 days Chemically, carbasone is p carbaminophenyl arsonic acid and contains 28 85 per cent of arsenic The toxicity of this drug is much greater than that of vioform or diodoquin and the occurrence of nausea or exacerbations of diarrhea is more commonly encountered than with the iodoxyquinoline derivatives

Oral Aldersone In 0 25 gm enteric-coated capsules a pentavalent arsenical has been recommended for the treatment of amebiasis by certain Latin American investigators It is used, as is carbasone, and in the opinion of the authors, the reports do not indicate any special advantage over carbasone

EMETINE Emetine is one of the two alkaloids (the other being cephaeline) of ipecac, the root of a Brazilian plant According to Windhaus, emetine is probably an isoquinoline derivative As with the iodoxyquinoline

derivatives, emetine is not especially effective against *E histolytica* in the test tube (Allan and Dale and Dobell) but is effective in vivo

Emetine Bismuth Iodide This contains about 20 per cent emetine and may be administered orally It was recommended first by DuMez and has been used chiefly by some of the British workers It does produce some gastric irritation and on occasion emesis may result Dosage 0 2 gm daily administered with meals for a period of 4 days

Chaparro Armargosa An emetine alkaloid derived from a Mexican cactus this may be used as a fluid extract in doses of 1 teaspoonful three times daily for a period of one week This also may produce gastric irritation and is best given with meals Practically none of this drug is available in this country and the authors have employed it on only one occasion

Emetine Hydrochloride Administered intramuscularly this acts as a cumulative protoplasmic poison *It is especially effective* in amebiasis when there is evidence of tissue invasion It is highly toxic, fatalities have been reported as well as numerous reports in which definite evidence of myocardial changes as manifested by electrocardiographic alterations have taken place These reports suggest that toxic effects begin to be manifest usually after the administration of 240 to 300 mg in a 4 to 5 day period When used intramuscularly and/or subcutaneously, despite care in selection of the injection site, tissue necrosis and sterile abscess formation may occur Various procedures have been recommended injection of 30 mg twice daily, injection of 60 mg once daily, etc It is the consensus that not more than 600 mg should be administered in a 10 day interval In view of the cumulative effect of the drug some clinicians have preferred to give more frequent short courses of emetine, stopping for example after 300 mg have been given in a 5 day interval In patients with concomitant cardiac pathology and in patients in the older age group, electrocardiograms taken before and at intervals during therapy may serve to indicate the occurrence of any toxic effect on the myocardium at the earliest possible moment If electrocardiographic changes (i e, depression or inversion of T waves, decreased amplitude of QRS deflection, changes in conduction time or changes in ST segment deflection) do appear, the drug should be stopped Matter reported that emetine appeared in the urine within 20 to 40 minutes after injection It can continue to be detectable in the urine for 5 to 9 weeks after therapy has been completed implying "some kind of stable deposit in the body, perhaps at the site of injection"

ANTIBIOTICS *Bacitracin* This may be had in 10 000 unit tablets for oral use A final recommendation as to daily dosage level can not as yet be made. Good reports have been made with daily doses ranging between 50 000 and 100,000 units daily Apparently no toxic effects have been reported after using the drug orally even for long periods of time In our hands with only a limited series of observations on a few patients 100,000 units daily for a 10 day interval seemed to produce results equivalent to those obtained with some of the iodoxyquinoline derivatives

Streptomycin Administered orally, streptomycin has the ability to alter the bacterial flora of the gastro intestinal tract Various combinations of streptomycin have been used by the writers with satisfactory results The efficacy of these preparations appears to be related to its effect on the bacterial flora of the intestinal tract because in in vitro observations amebic growth is not appreciably

... r investi

... otomycin

Penicillin Penicillin may alter bacterial flora of the gastro intestinal tract whether administered orally or parenterally The inactivation of penicillin by the penicillinase elaborated by the colon bacillus makes it a poor selection as a therapeutic agent

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have appeared As with other ... amebic growth is not inhibited in the test tube The action in the gastro intestinal tract in terms of altering the established flora thereby creating a growth environment incapable of allowing *E histolytica* to survive is the probable mode of action We have used aureomycin in doses of 0 250 gm every 6

hours for periods of 2 weeks in a limited group of patients It is too early to evaluate any long term results The absorption from the gastro intestinal tract would appear to make aureomycin one of the three such amebacidal agents (emetine and chloraquin being the other two) worth considering for administration to patients with evidence of tissue invasion

Chloromycetin Chloromycetin would ap pear to have a role in the therapy of amebia sis in terms of its effects on the bacterial

SULFONAMIDES A few reports have ap peared suggesting some usefulness to the employment of the poorly absorbed or non-absorbable sulfonamide preparations such as sulfaguanidine and succinylsulfathiazole Their mode of action probably is related to the inhibition of amebic growth resulting from alteration of the bacterial flora of the intestinal tract The dosage varies between 6 0 and 12 0 gm a day

CHLORAQUINE DIPHOSPHATE (7 chlora 4 [4 diethylamino 1 methylbutylamino quino line diphosphate]) This is one of the newer antimalarial drugs It is almost completely

lungs Approximately 10 to 20 per cent of the drug can be recovered in the urine, the re-mainder being metabolized by the body Headache of varying severity, pruritis and blurring of vision are some of the toxic manifestations Manson Bahr reviews cases of amebiasis treated with chloraquine, in cluding a case of amebic hepatitis which was refractory to treatment with other drugs A

propriate in the treatment of patients with evidence of tissue invasion

General Comment The chief controversy

agreement that when one variety of ameba-cide does not work then another should be tried Many of the recommendations obvi-ously are quite arbitrary and represent em pirical thoughts on the subject rather than critical evaluation of scientific evidence

It seems to be the consensus that in the presence of hepatic amebiasis, hepatic ab scess, or other sites of extragastro intestinal tract involvement, emetine is the drug of choice The weight of opinion favors emetine as the preferred drug in the case of early amebiasis with acute dysentery and fulminat-ing symptoms Most dissonant are the dis cussions as to the use of emetine in the chronic milder forms of the disease The writers do not wish to make any dogmatic recommendations In our use of the drug, however, we reserve emetine for those pa tients with evidence of an active phase of tissue invasion The severity of the diarrhea and of the proctoscopic findings, the pres ence of a positive complement fixation test, and the evidence of extragastro intestinal in volvement are some of the criteria that enter into the problem A large part of the decision is also based on judgment, and unfortunately there is no associated laboratory test which determines its application

If a decision to use emetine has been made,

be at bed rest during therapy, especially those individuals in the arteriosclerotic age group, serial electrocardiograms should be taken so that toxic effects on the myocardium can be promptly detected, and therapy dis continued or reduced in intensity if neces sary

Our own opinions as to the choice of amebacides may be summarized as follows

(1) If tissue invasion is present as evi-denced by the proctoscopic findings, blood and mucus in the stools, extra-gastro intestinal tract involvement, and a positive complement fixation test, the administration of an ame bacidal agent which is not absorbed from the gastro intestinal tract is not

of appreciable value Emetine aureo

(2)

sion any of the lumen acting drugs may be selected

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FLAGELLATE DYSENTERY

Giardiasis Giardiasis as a clinical entity in the light of present knowledge implies nothing more than the presence of the protozoan *Giardia lamblia* (*Giardia intestinalis*) in the intestine According to reports it apparently occurs more frequently in children than adults but its identification in the stools of children or adults cannot be correlated with the occurrence of digestive symptoms A significant group of patients was reported by Hartman and Kyser at the Mayo Clinic in which digestive symptoms improved after the institution of therapy These data are difficult to evaluate but in the writers experiences the conclusion was forced upon them that Giardia represent luminal parasites which are nonpathogenic No treatment is recommended *In view of the equivocal* aspects of the clinical significance of this protozoan if for any reason therapy is desired the principles have already been out*lined in the discussion of amebiasis* Hartman and Kyser have recommended the use of

amebacidal drugs are not as efficient as in the treatment of amebiasis which might well be due to the fact that the usual habitat of *Giardia lamblia* is the upper small intestine rather than the large bowel as in the case of amebae The same opportunity for the effect of the amebacidal drugs on the bacterial flora of the large bowel probably does not prevail

Balantidiasis In contradistinction to the foregoing flagellate *Balantidium coli* is known to produce ulceration and tissue invasion in the colon of man Manlove Strong Walker and Lynch have reported on these occurrences Walker found that in experimental infection of monkeys with organisms from man and swine *Balantidium coli* had the ability to penetrate normal intestinal mucosa producing ulceration of the submucosa and muscularis As in amebiasis the cecum is one of the predominant sites of involvement Acute fulminating symptoms with blood and mucus in the stools may occur or the manifestations may be chronic and low grade in character as in amebiasis In some instances as in this disease *Balantidium coli* may exist as a luminal parasite with no symptoms or findings attributable to its presence Specific treatment is somewhat uncertain

Rectal instillations have been recommended by numerous workers The instillations have included quinine (1 1000 solution) (Dobell) quinine hydrochloride (0 75 gm in 300 cc water), iodine solution

(1 10 000 solution) silver nitrate (1 3000 solution) It would seem reasonable to assume that if the cecum is the most frequent primary site of invasion rectal instillations would accomplish little toward eradication of the parasite This has been the experience at least as far as amebiasis is concerned and rectal instillation of medication for this disease has largely been abandoned

ORAL THERAPY Oral administration seemingly is more logical both in terms of possibly preventing growth of the organism by

cides seem worth using plus quinine atabrine and as suggested by Haughwout Domingo and deLeon a 20 per cent alcoholic solution of benzyl benzoate given in doses of 30 drops the first day 45 drops the second day and 60 drops the fourth day In their case report the medication was continued for 22 days the patient dying on the 33d day of an allegedly unrelated disease In view of the known highly toxic effects of benzyl benzoate the drug should be used with caution

TRICHOMONIASIS The occurrence of *Trichomonas hominis* in the stools of man as in the case of *Giardia lamblia* has dubious significance Many reports have been reviewed by Lynch and the reader is referred to his text for a more detailed discussion The consensus is that this flagellate protozoan is a luminal parasite and its presence does not correlate with the occurrence of symptoms or intestinal lesions

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DISEASES OF DOUBTFUL ORIGIN

ERYTHEMA NODOSUM

Erythema nodosum is now generally thought to be one of the diffuse collagen diseases that result from hypersensitivity Infections of the upper respiratory passages tuberculosis rheumatic fever coccidiodomycosis and such medicaments as the halides and sulfonamides have been mentioned as etiologic agents It is interesting to note that in European countries the disease is usually thought to be related to tuberculosis whereas in this country more stress is placed on infections of the upper respiratory passages

Treatment of this disease is directed primarily to correcting or removing the etiologic factor or factors involved Infections of the upper respiratory passages should be appropriately treated The presence or absence of tuberculosis or coccidiodomycosis should be determined The halides sulfonamides and related preparations should be avoided

Bed rest is a most important factor in

to disappear in the recumbent position In general bed rest should be maintained until the patient has been afebrile for at least a week and until the sedimentation rate has fallen to within normal limits and provided no new lesions have formed It is most important to demonstrate the absence of any cardiac involvement because of the frequent association of erythema nodosum and active rheumatic fever

Particular care should be taken to protect the involved extremities The nodules may be extremely painful and in instances even the weight of the bedclothes may be intol

erable A heat cradle is usually satisfactory for supporting the bedclothing Heat itself gives a certain measure of relief

Analgesics are indicated when the pain is severe Salicylates are the drugs of choice for the analgesic as well as the antipyretic effect There is some evidence that large doses of salicylate (sodium salicylate, 20 grains q i d, or 1 2 gm) tend to shorten the course of the disease

There is some indication that the antihistamines may either cure or greatly shorten the course of the disease Pyribenzamine (50 mg t i d) is the drug that has been used most frequently

It should be pointed out that erythema nodosum may remain active for periods of several weeks to months and that frequently patients become discouraged with their apparent lack of progress An awareness of this problem by both physician and patient does much to simplify some of the problems of morale which may otherwise make proper care difficult

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DISSEMINATED LUPUS ERYTHEMATOSUS

Disseminated lupus erythematosus is a generalized systemic disease which occurs in acute, subacute, and chronic forms It occurs in females in 60 to 80 per cent of the cases, usually in the second and third decades of life

Drugs have been utilized with equivocal results It is difficult to evaluate the treatment in a disease which is chronic in nature and subject to remissions and exacerbations

Gold colloid has long been the favorite remedy of dermatologists in the chronic form of this disease The results have been uniformly poor Schmidt, in 1947, treated a series of cases with colloidal gold sulfide in conjunction with vasodilators He theorized that the poor results in previously treated groups were due to vascular spasm at the site of the lesion and failure of the gold to reach the unhealed active lesions Results in his series were gratifying He recommends an initial dose of 2 cc of colloidal gold sulfide, by either the intravenous or intramuscular route This is increased to 3 cc and even 4 cc at intervals of 4 days after which 5 cc should be administered every 5 to 6 days To increase vasodilatation, 100 mg of nicotinic acid are taken after each meal and an additional 100 mg 5 minutes before the injection of the gold compound

Bismuth, by the intramuscular route is also utilized in the treatment of the chronic form of the disease The results again are controversial Sawicky, in 1947, recommended the use of oral bismuth (sodium bismuth triglycollanate) His results were not impressive

The heavy metals should be used with caution and should be avoided in the acute forms of the disease because of their tendency further to depress the bone marrow function and increase the severity of the renal damage The treatment of acute disseminated lupus erythematosus at the present time is even more hopeless than the treatment of the chronic varieties Bed rest is essential Exposure to light tends to exaggerate the disease Hence the patient should be kept in a darkened room A high vitamin intake is usually recommended, although there is no reason to believe that this favorably alters the course of the disease Because of the tendency of this disease to occur in females during the childbearing years an endocrine factor has long been suspected Large doses of estrogens, androgens and even castration have not altered the course of the disease

Penicillin, streptomycin, and the sulfa drugs have no effect although they are recommended for the treatment of secondary infections Some clinicians recommend the use of these drugs prophylactically to prevent the secondary infections that are prone to occur in this disease

In view of the widespread involvement generally observed in disseminated lupus numerous nonspecific therapeutic measures are in order although the disease process will not be altered Treatment of the cardiac and renal involvement by attention to electrolyte requirements, and administration of oxygen are in order

Some of the recent studies by Rich and his co workers suggest an allergic basis for the disease and classify lupus as one of the diffuse collagen diseases along with periarteritis nodosa, rheumatic fever, and hypersensitive serum and drug reactions The use of anti

histaminic drugs has not favorably influenced the course of the disease up to the present time

The recent use of cortisone (adrenocortical hormone factor E) by Hench and his co workers and the use of the adrenocorticotropic hormone of the pituitary (ACTH) may be expected to influence favorably the course of the disease

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INFECTIOUS PLEURODYNIA

Infectious pleurodynia is a disease which occurs in epidemics and is characterized by fever headache and severe pain over the area of attachment of the diaphragm The etiology is unknown but it is thought to be due to a filtrable virus

There is no specific treatment The pyrexia and severe chest pain are usually controlled by large doses of salicylates (1 to 1 5 gm every 4 hours) In severe cases morphine sulfate 15 mg by hypodermic injection may be necessary The local application of heat gives some measure of relief A chest binder may be resorted to particularly if an associated cough exaggerates the pain

The disease is self limited and usually runs its course in 4 to 10 days One or more recurrences are common

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REITER S DISEASE

This triad of polyarthritis urethritis and conjunctivitis is of unknown etiology The disease is self limited one or more recurrences are not uncommon

Penicillin and sulfonamides do not alter the course of the disease the treatment therefore is chiefly symptomatic

The joint involvement is usually multiple and the pain may be severe Heat and massage give some measure of relief Salicylates (1 to 1 5 gm every 4 hours) may also decrease the joint pain Physical therapy should be started early to prevent deformity

The eyes should be cleansed frequently with boric acid solution

Bland urethral irrigations (1 6000 permanganate of potash or 1 10 000 oxycyanide of mercury) and hot sitz baths have been recommended for the genito urinary infection

Gold therapy has been suggested in the treatment of this condition The toxicity of this drug however hardly justifies its use in a self limited disease

Fever therapy either by an induction cabinet or foreign protein injection may be helpful

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RELASPING FEBRILE NODULAR NON SUPPURATIVE PANNICULITIS
(Weber Chr st an D sease)

Relapsing febrile nodular panniculitis is a rare disease characterized by recurrent bouts of fever associated with nonsuppurative inflammatory nodules of the subcutaneous tissues

The treatment is usually symptomatic No specific therapy is known Arnold reported on a case which apparently responded to [illegible] case which failed to respond to penicillin

Because of the rarity of the disease and the tendency to remissions reports of cures in isolated cases should be looked on with suspicion

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TERRAMYCIN *

Terramycin, a new antimicrobial agent produced by the growth of the mold, *Streptomyces rimosus*, is a highly stable insoluble crystalline amphoteric substance which can be reacted chemically with certain acids and bases to form stable water soluble crystalline salts (Finlay et al) It is effective in vitro and *in vivo against a* wide variety of microorganisms, including many of the gram positive and gram negative bacteria both aerobic and anaerobic the rickettsiae and certain of the viruses (Hobby et al , Snyder, Rose) It is especially effective *in the treatment of* all forms of pneumonia (including primary atypical pneumonia), in acute brucellosis, and in urinary tract infections due to terramycin sensitive organisms as well as in certain other bacterial rickettsial and viral like infections

Pharmacology ABSORPTION AND EXCRETION *Terramycin and its salts are substances* of relatively low toxicity Terramycin is absorbed readily following either parenteral or oral administration in animals and man (Hobby et al , Herrell et al , Welch et al Werner et al) When the antibiotic is administered by the oral route, more rapid absorption and higher concentrations of terramycin are observed *in the serum of* patients receiving terramycin hydrochloride than in those receiving the amphoteric form (Hobby et al , Welch et al) For this reason, terramycin generally is administered orally in the form of terramycin hydrochloride

The serum content of terramycin is maintained at a fairly constant level for several hours after the oral *administration of single* 1 gm doses The concentration begins to decrease about 6 hours after administration of such doses but activity frequently may be demonstrable in the serum for more than 24 hours Therapeutically effective serum levels of terramycin may be maintained in adults when 1 to 1 25 gm of terramycin are administered *orally once every 6 hours In infants,* 33 mg per kilogram of body weight are required to produce concentrations of 0 5 to 1 5 micrograms of terramycin per millimeter of serum, while single doses of 66 mg per *kilogram of* body weight produce levels of 1 0 to 4 0 micrograms per millimeter of serum (Hunt et al)

Terramycin diffuses readily through the placenta and is present in the fetal circulation *When therapeutically effective amounts* are present in the blood serum, terramycin diffuses into the pleural fluid Preliminary observations have suggested that terramycin may not diffuse readily into the cerebrospinal fluid when therapeutically effective blood serum levels are maintained Hall and his associates, however, have reported one *case of an infant with pneumococcal meningitis* who responded satisfactorily following

into the cerebrospinal fluid Hunt et al have demonstrated furthermore that concentrations of 0 4 microgram of terramycin per *milliliter of spinal fluid may be detected in* infants receiving single doses of 66 mg of terramycin per kilogram of body weight and showing serum levels of 1 0 microgram per milliliter

Terramycin appears to be concentrated in the hepatic system and is excreted in the bile It is excreted in urine and in high concen*trations, in the feces in a biologically active* form

TOXICITY Terramycin hydrochloride may be administered orally in large dosages with no signs of toxicity, nonetheless, unlike penicillin, a maximal dosage exists beyond which it cannot be administered parenterally without toxic manifestations No toxicity has been *observed in animals receiving* terramycin hydrochloride in dosages of 80 to 500 mg per kilogram of body weight for prolonged periods of time When administered parenterally, however, some signs of toxicity are apparent in animals when daily dosages of 80 to 100 or 160 mg of sodium terramycin or terramycin hydrochloride per kilogram of body weight are administered intramuscularly over prolonged periods of time (P'an et al, Lepper et al)

The maximal single *dose of terramycin* hydrochloride which has been administered to humans is 3 25 gm (49 mg per kilogram of body weight), the maximal daily *dose is* 15 gm , the maximal total dose, 368 gm No

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* Because of the relatively recent development of *terramycin it is hoped that this special section will* make a valuable supplement to the preceding chapter on Infectious Diseases —*Editor*

untoward reactions, other than nausea, vomiting, and loss of weight after administration for prolonged periods of time, have been observed in a limited number of patients who have received 12 to 15 gm daily by the oral route It is believed, however, that these dosages represent the maximal quantity that should be used in man

In patients receiving 1 to 5 gm daily, mild gastro intestinal disturbances have been noted in some instances The most common reaction is mild looseness of the stools, which in most infectious diseases has a favorable effect In occasional instances, mild nausea or vomiting may occur, this generally occurs when the drug is administered on an empty stomach and often may be avoided by its *administration with cold milk or a light* meal In those patients experiencing nausea [illegible]

relationship to the size of the daily dose, *such reactions are rarely observed with dos*ages of 1 to 3 gm per day

There is no evidence that any impairment of renal or liver function occurs when daily oral dosages of 1 to 6 gm are used Likewise white blood cell and differential counts remain normal during therapy and there is no evidence that terramycin exerts any abnormal effect on the bone marrow Glossitis, *with and without lesions, may occur occa*sionally Reactions of an allergic nature, likewise, have been observed in a few instances Mild allergic reactions and those responding to the usual treatment of such conditions are not contraindications to the further administration of the antibiotic

Dosage and Administration Sufficient data are not available to permit a statement of the minimal or optimal dosage required for the treatment of all of the infectious diseases which may respond to the administra- [illegible]

and tissue fluid concentration of terramycin which is adequate to control the infection promptly, and maximal dosage from onset of therapy, therefore, is desirable

In general, it is believed that 2 gm daily, in divided dosage once every 6 to 8 hours, is adequate for the treatment of most acute infections Further evaluation may indicate that 1 to 1 5 gm daily may be sufficient for control of certain mild infections or those due [illegible]

It is well known that higher dosages of penicillin on a per kilogram of body weight basis, must be used in infants and children than in adults, if comparable concentrations of antibiotic are to be attained in the blood serum and tissues This is true of terramycin also Dosages of approximately 100 to 150 *mg of terramycin per kilogram of body* weight per day are indicated in the treatment of infections in infants, while adult sized dosages may be used for older children

Terramycin should be administered by the oral route only Full dosage should be given

TABLE I

SUMMARY DATA OF 150 TERRAMYCIN TREATED PATIENTS

Diagnosis	*No of Patients*	*Result*
Brucellosis	12	Excellent
Typhus	5	Good
Typhoid	6	Doubtful effect
Paratyphoid	2	Doubtful effect
Amebiasis	2	Excellent
Anthrax	1	Excellent
Smallpox	1	No effect
Pneumococcal pneumonia	60	Excellent
Unclassified bacterial pneumonia	20	Good
Urinary tract infections		
Strep fecalis	1	Excellent
E coli	6	Excellent
A aerogenes	2	Excellent
B proteus	8	Poor
Ps aeruginosa	2	Poor
Paracolon bacillus	1	Poor
Erysipelas	2	Excellent
Streptococcal pharyngitis	3	Excellent
Pulmonary tuberculosis	3	No effect
Influenza	2	No effect
Measles	3	No effect
Regional ileitis	3	1 Excellent 2 No effect
Ulcerative colitis	1	No effect
Malaria (*P vivax*)	1	No effect

(From Knight, V *New York State J Med*, 1950)

for at least 48 hours after the temperature becomes normal and acute symptoms have subsided, diminishing dosages are recommended for an additional 48 hours thereafter

Diseases in Which Terramycin Is Effective PNEUMONIA Terramycin may be used satisfactorily in the treatment of essentially all cases of pneumonia *Owing to its*

Pneumococcal (Lobar) Pneumonia, with and without Bacteremia Terramycin has been used extensively, by a number of in

series of 60 patients, whose distribution according to age sex, and causative type of pneumococcus compared closely to groups which he had treated in previous years with penicillin, observed marked improvement in 59 of the 60 patients with almost complete defervescence within 24 hours after institution of terramycin therapy (5 gm daily) One patient only in this series failed to respond to therapy and died after 4 days of treatment, at necropsy this patient showed evidence of acute rheumatic fever as well as left lobar pneumonia According to Timpanelli patients with signs of pleural fluid or pleurisy *on admission responded readily to* terramycin therapy, without requiring drainage Twenty per cent of these patients were bacteremic *at the onset of therapy* There were no cases of pneumococcal meningitis or other purulent complications, following terramycin therapy, within this group of 60 patients Subsequent studies by Timpanelli and his associates, Tillett et al, and Dowling et al, have indicated that similar satisfactory results may be obtained with lower dosages

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treatment of this infection In order to minimize the possibility of relapse, it is advisable to continue therapy for periods of 5 to 10 days, depending on the nature and severity of the infection

Primary Atypical Pneumonia Good therapeutic *results* have been obtained in the treatment of primary atypical pneumonia when terramycin has been used in dosages *ranging from 2 to 5 gm* daily (Melcher et al, Spink, Martin) In general 2 gm daily in divided dosage is adequate, the response is prompt and in most instances the temperature returns to normal within 24 hours

Friedlander's Pneumonia Little information is available concerning the effect of terramycin in the treatment of pneumonia due to Friedlander's bacillus (*Klebsiella pneumoniae*) The causative organism however, is highly sensitive in vitro to the action of this antibiotic (Hobby et al) Four recorded cases of proved Friedlander's pneumonia, 2 of these having failed to respond to *other forms of antimicrobial therapy*, showed defervescence and complete resolution within 5 days after initiation of treatment (4 gm of terramycin daily in divided dosage once every 4 hours for 7 to 10 days)

Mixed Bacterial Pneumonias Terramycin may be used clinically in the treatment of most cases of primary pneumonia due to mixed bacterial floras (*Staphylococcus aureus, Streptococcus haemolyticus, Streptococcus viridans, D pneumoniae, H Influenzae, N catarrhalis*, etc) In a series of 20 patients, Timpanelli and his associates observed satisfactory responses following administration of this agent In general however, defervescence occurred more slowly than in patients with pneumococcal pneumonia

COCCAL INFECTIONS *Streptococcal Infections, with and without Bacteremia* Most *strains of hemolytic and nonhemolytic* streptococci, including the enterococci (*Streptococcus faecalis*), which are resistant to other *antimicrobial agents, are highly* susceptible to the antimicrobial action of terramycin Infections due to hemolytic streptococci, such as septicemia, erysipelas, puerperal sepsis, scarlet fever, acute follicular tonsillitis, septic

with this antimicrobial agent Although ex tensive data are not available to date on the action of terramycin against infections due to nonhemolytic or anaerobic streptococci one case of a perirectal abscess due to anaerobic streptococci has been reported which showed a prompt response following administration of terramycin in a daily dosage of 2

gm In another individual with subacute bacterial endocarditis caused by a microaerophilic streptococcus fall in temperature and symptomatic improvement resulted on administration of 4 to 6 gm daily Prompt symptomatic and bacteriologic responses likewise have been observed in a limited number of patients with chronic pyelonephritis and urinary tract infections due to the enterococci

Staphylococcal Infections Rantz and his associates have reported that 30 strains of penicillin resistant staphylococci when tested in vitro for their sensitivity to terramycin have shown a remarkable degree of susceptibility to this agent Infections due to terramycin sensitive strains of *Staphylococcus aureus* including septicemia endocarditis cellulitis acute and chronic sinusitis bilateral purulent otitis media furunculosis impetigo secondary infections associated with acne vulgaris conjunctivitis and urinary tract infections frequently respond rapidly to terramycin therapy (Blake et al)

Gonococcal Infections Clinical experience indicates that terramycin is highly effective in the treatment of acute gonorrheal urethritis Hendricks and his associates have demonstrated that two 1 gm doses administered orally at 6 hour intervals are sufficient to cure 100 per cent of patients while two 0 5 gm doses administered at 6 hour intervals are capable of controlling approximately 80 per cent of patients treated Schoch and his associates on the other hand report that a single 1 gm dose is sufficient to cure essentially all patients with acute gonorrhea According to these investigators re treatment with 0 5 gm once every 6 hours for 3 to 4 doses (i e 1 5 to 2 0 gm) is recommended if the response is not prompt

There is no evidence to date as to whether terramycin is effective in the treatment of chronic gonorrhea or cases with complications such as arthritis prostatitis epididymitis or salpingitis it seems likely however that it should be effective

Meningococcal Infections Little information concerning the effect of terramycin in the treatment of meningococcal infections is available Preliminary evidence suggests that in some instances terramycin may be adequate for control of meningococcal meningitis Further studies are necessary to evaluate its true effect in the treatment of this disease Meanwhile sulfadiazine remains the drug of choice However in severe or overwhelming infections terramycin or penicillin or both antibiotics should be given in addition

BACILLARY INFECTIONS *Brucellosis (Undulant Fever)* In vitro studies by Spink and his associates and by Heilman et al have indicated that terramycin is highly effective against *Brucella abortus* *Brucella suis* and *Brucella melitensis* and is capable of exerting a marked suppressive effect on the course of experimental brucellosis in mice Clinical experience with terramycin indicates that this antibiotic is also highly effective in the

verity of illness within a few hours after initiation of terramycin therapy in 11 of 12 proved cases Nine of these were bacteremic (*Brucella melitensis*) while the remainder showed significant elevations of antibody titer Nine of these patients were febrile on the first day of therapy in these defervescence was rapid (average 1 9 days) All patients were ambulatory within one week after beginning therapy although many of them had been severely ill for more than one month Bacteremia disappeared at the time of defervescence in some patients but persisted for 3 to 6 days in others The one individual patient who failed to show a definite response during therapy was a patient in whom extensive bony involvement was present The dosage used throughout this series was 100 to 150 mg per kilogram of body weight per day until the patient was afebrile then 50 mg per kilogram per day for a total of 28 days of therapy None of these patients relapsed during follow up periods ranging from 2 to 8 weeks

In a subsequent series of 4 patients Marones observed an initial good response on administration of similar doses of terramycin for 5 to 7 days only In all instances however relapses occurred following discontinuation of therapy Prolonged therapy *therefore* is essential in order to minimize the possibility of relapse

No data are available on the effect of terramycin in the treatment of chronic brucellosis

Infections Due to Terramycin sensitive

treatment of acute infections such as septicemia multiple liver abscesses diffuse bronchopneumonia etc due to *E coli* *A aerogenes* and other terramycin sensitive gram negative organisms It is particularly effective in the control of certain urinary tract infections Ball and Douglas have reported that a dosage of 250 mg administered orally once every 6 hours for 5 days followed by 125 mg once every 6 hours for an additional 5 days is sufficient to produce a prompt and effective response provided the invading organisms are susceptible and no organic or obstructive disease exists

*King and his associates report similar ben*eficial results in the treatment of pyelonephritis and postprostatectomy urinary tract infections on administration of 500 mg once *every 6 hours for 5 days According to these* investigators this regimen is adequate for the treatment of infections due to *A aerogenes* *E coli* the enterococci *Ps pyocyaneus* and *Staphylococcus aureus* Although *Proteus vulgaris* an organism frequently present in urinary tract infections generally cannot be eliminated some improvement often results when terramycin is administered to patients with mixed infections involving this organism

Hemophilus Infections Experimental studies in vitro and in animals indicate that *H influenzae* and *H pertussis* are highly sensitive to the action of terramycin In a

24 to 72 hours after initiation of therapy (500 mg once every 6 hours) (King et al)

Miscellaneous Infections Preliminary evidence suggests that terramycin may be used with satisfactory therapeutic results in the treatment of anthrax and other gram positive bacillary infections tularemia and bacteroides bacteremia

SPIROCHETAL INFECTIONS *Syphilis* Sufficient data are not available to indicate the true value of terramycin in the treatment of syphilis According to Hendricks et al clinical healing of syphilitic lesions (primary and early secondary syphilis) occurs promptly when dosages of 60 mg per kilogram of body weight per day are used for a period of 8 days In essentially all instances the dark field is reversed within 24 to 48 hours Two patients who were serologically positive (Eagle precipitation test) at the onset of therapy sho ed negat e ... one mon

RICKET

tory studies by Snyder and Smadel indicate that terramycin is a highly effective antirickettsial agent against *R tsutsugamushi* (scrub typhus) and *R prowazeki* (epidemic typhus) Knight and his associates have reported 5 patients with typhus (2 murine 3 epidemic) who were treated with terramycin in dosages of 100 mg per kilogram per day With the exception of one patient whose *temperature reached normal only after* slightly more than 96 hours all were afebrile and convalescent within less than 54 hours after initiation of therapy Marones has re*ported a similar response in 5 additional pa*tients within 48 hours after initiation of therapy A single patient with scrub typhus showed a striking response following ad*ministration of a single 3 gm dose (Smadel)*

Rickettsialpox Laboratory and clinical studies by Rose and his associates indicate that terramycin is highly active against *R akari* the etiologic agent of rickettsialpox A therapeutic response may be observed within 24 to 48 hours following the administration of daily dosages of 2 to 5 gm

VIRAL LIKE INFECTIONS *Granuloma Inguinale* A limited series of patients with granuloma inguinale has been treated with terramycin in dosages ranging from 1 5 to 4 gm per day According to Hendricks et al degeneration of the Donovan bodies and clinical healing of granuloma inguinale lesions occur promptly when dosages of 60 mg per kilogram of body weight are used daily for periods of 10 days

Lymphogranuloma Venereum Although the data available are limited preliminary evidence suggests that terramycin is effective in the treatment of lymphogranuloma venereum

Miscellaneous Viral like Infections Although it has not been possible to demonstrate that terramycin exerts a specific antiviral action against the virus of herpes zoster preliminary observations indicate that

may be of value in the treatment of some ases of herpes zoster Preliminary evidence uggests also that terramycin is of value in he treatment of infectious mononucleosis

Experimental studies indicate that in high oncentrations terramycin is capable of inibiting the infection of the chick embryo vith the PR8 strain of influenza A virus It ias not been possible to demonstrate this ffect in experimentally infected mice Nonetheless, administration of terramycin to patients with influenza in most instances auses rapid reduction in fever and symp omatic improvement (Finland)

PROTOZOAN INFECTIONS *Amebiasis* Terra nycin has been used effectively in the reatment of over 235 patients with amebia is According to Most and Van Assendelft,

plete disappearance of *E histolytica* from the stools of all but 1 of 16 carefully con trolled patients Parasitic relapses occurred in the 16th patient on the 11th day after discontinuation of treatment In the remain ing 15 patients an average of 4 2 stools per patient remained negative during observa tion for an average of 19 4 days of therapy

MISCELLANEOUS INFECTIONS *Upper Respiratory Infections* Terramycin is excreted in high concentration in the sputum and appears to exert a marked effect on the nature and consistency of the sputum as well as on its bacterial content In cases of acute bronchitis pharyngitis laryngotracheitis, tracheobronchitis, sinusitis, and otitis media, and in chronic bronchiectasis and whooping cough, administration of terramycin often results in prompt symptomatic improvement Upper respiratory infections, with cough, fever, and hoarseness frequently respond promptly to terramycin therapy Although there is probably no specific action of the antibiotic on the influenza virus in human subjects, marked symptomatic improvement occurs in patients with influenza within 24 to 48 hours after initiation of terramycin therapy

Reduction of Fecal Flora Preoperatively and Postoperatively Terramycin is active against gram positive and gram negative micro-organisms, both aerobic and anaerobic, and against the enterococci It is extremely effective, therefore, in reducing the bacterial flora of the feces and may be used advantageously for this purpose preoperatively and postoperatively (Rantz, Pulaski)

Peritonitis The broad antimicrobial spectrum of terramycin makes it exceptionally useful as a chemotherapeutic agent for the control of peritonitis due to mixed bacterial floras (Yeager)

Achlorhydria Striking symptomatic improvement frequently occurs following ad ministration of terramycin in older debilitated patients with achlorhydria who show con stant gastro intestinal symptoms (i e, gas distention, and constipation) due to bacterial growth ascending into the small gut

Diseases in Which Terramycin Is of Doubtful Value Terramycin has been used extensively in the treatment of typhoid fever and other Salmonella infections In patients with typhoid fever, there has been no evidence of a drug induced response (Knight) In patients with other types of Salmonella infection, more satisfactory therapeutic results may be obtained (King et al , Knight)

Experimental studies in vitro and in vivo indicate that most strains of *Ps pyocyaneus* are highly resistant to the action of terramycin Occasional patients with such infection have responded to therapy, however, and the role of terramycin in the control of infection due to this organism remains to be evaluated

No clinical data are available concerning the action of terramycin in the treatment of Rocky Mountain spotted fever or Q fever Laboratory studies on this group of organ isms suggest, however, that terramycin should be effective in their control (Yeager et al)

Diseases in Which Terramycin Is Ineffective Terramycin is ineffective in the treatment of measles, mumps, malaria, trichinosis, arthritis, chickenpox, and variola Although experimental studies indicate that terramycin may possess tuberculostatic activity, there is no evidence to date that it is effective in the treatment of tuberculosis in man The use of terramycin in the treatment of these infections is not indicated

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PARASITIC DISEASES

FLUKE INFECTIONS OTHER THAN SCHISTOSOMIASIS

The flukes are a group of worms, leaf-shaped, varying in size from 1 to 75 mm in length

From the standpoint of therapy, flukes in man can be divided into two groups those found in the intestinal lumen, and those occurring in tissues and, therefore, more resistant to the action of the usual anthelmintic drugs It is natural that vermifuges have been used in the treatment of intestinal flukes, usually with considerable effectiveness For example, *Fasciolopsis buski* infections may be treated by giving two doses of 0 2 gm of beta naphthol or by carbon tetrachloride administered as for hookworm infections Treatment of infections with Heterophyes and Metagonimus tetrachlorethylene, as described in this book under Hookworm Disease is recommended

In infections with somatic parasites the [illegible]

protozoan somatic infections are emetine antimonials, and gentian violet these drugs are given parenterally

Paragonimus infections are acquired by eating raw crayfish or certain fresh water clams Although the parasite occurs in the United States, human cases are not encountered here because of our dietary habits The disease is a serious one in that the flukes invade the lungs, producing a clinical picture much like that of pulmonary tuberculosis The disease is readily distinguished from other pulmonary infections however, by the presence of the characteristic eggs in the sputum Specific treatment is generally unsatisfactory, although success has been reported with the use of sodium antimonyl tartrate, and Yokogawa et al reported cures in some cases treated with prontosil and emetine The symptoms of the disease generally subside in 5 or 6 years after the infection has been acquired and removal from exposure has been beneficial

Fasciola infections are acquired by eating aquatic plants with encysted larvae Human cases occur from this source in many parts [illegible] narily the adults are found in the bile passages Treatment is not satisfactory, oleoresin of the male fern (aspidium) as used for tapeworm infestation or 1 per cent Magdala rose dye given intravenously has been recommended, emetine and carbon tetrachloride may be beneficial

Opisthorchis and Clonorchis infections are acquired by eating raw infected fish Adult worms are found in the bile passages Sodium antimonyl tartrate given intravenously and oral gentian violet in enteric coated tablets may be of value

Prevention These flukes occur in the Orient in parts of Africa and a few cases have been reported from Europe They are all acquired by eating fresh water aquatic plants or fresh water fish, crayfish, or clams The native food habits determine to a great extent the frequency of occurrence of these infections in man In many places, these foods are eaten raw or with inadequate pickling to kill the encysted parasites Americans traveling in these areas should be cautioned not to eat uncooked exotic foods whether served raw or spiced

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SCHISTOSOMIASIS

Schistosomiasis has become important in the continental United States within recent years because of the acquisition of the disease by members of the armed forces and because of its importation by foreign visitors

The organisms do not multiply within the body and the degree of illness is conditioned by the number of parasites acquired In severe cases the disease is incapacitating and may cause death Schistosomiasis is a major cause of illness in Puerto Rico

Schistosomiasis is acquired from bathing or wading in fresh water containing the cercariae or by ingesting cercariae with drinking water These cercariae are released from infected snails in enormous numbers, they are free swimming and attracted to man s skin on contact with water The cercariae penetrate the intact skin of the victim and after about 6 weeks they mature to become an adult worm in the venules of the liver, intestine, or bladder, depending on the species of schistosome Females in those locations deposit spined eggs in the wall of the venule whence they are carried passively to the lumen of the bile ducts intestine, or bladder The clinical disease is produced by the accumulative scarring due to the presence of and passage through tissues of the ova The ova may secrete a lytic substance that adds to the mechanical trauma

Chemotherapy cannot be expected to be of value in alleviating the symptoms produced by the tissue injury already present Chemotherapy should therefore be directed at killing the adult parasites so that more eggs will not be produced, and at killing the ova already in the tissues that may be secret-

rhosis which is commonly present and treatment of granulomatous or neoplastic tissues which are often found in the bladder or rectum

The chemotherapeutic agents of choice have been among the trivalent antimony compounds The antimonyl tartrates are most widely used because of their cheapness and effectiveness Less toxic and less irritating to the tissues are stibophen (fuadin manufactured by the Winthrop Chemical Company) and lithium antimonyl thiomalate (anthiomaline, manufactured by Merck and Company) The antimony tartrates must be given intravenously, stibophen and anthiomaline are given intramuscularly

Potassium antimonyl tartrate (tartar emetic) is more economical than sodium antimonyl tartrate and is generally preferred in this country Neither compound should be sterilized by heating The compounds are administered intravenously as aqueous or saline solutions up to 6 per cent in strength Because these salts are caustic to tissues, concentrations of 0 5 to 1 per cent are preferred and less injury occurs in case of extravasation The injections should be given over an interval of several minutes to avoid the immediate side reactions presumably due to the high blood levels which are produced with the faster administration

One per cent solutions of tartar emetic in 5 ml ampules are available from the Abbott Laboratories Solutions may be made up in sterile 5 per cent glucose in saline in physiologic saline, or in distilled water by weighing and adding tartar emetic from a freshly opened bottle of tartar emetic using sterile glassware Such solutions should be made up fresh each day

Various schedules of treatment have been used successfully, most regimens require three administrations weekly or, better, an administration every second day The following schedule is commonly used for adults of average weight The solution is given every second day for a total of 15 doses if 0 5 per cent solution is used 4 cc are given the first day and the amount increased at each injection by 4 cc to the largest amount of 28 cc by the sixth injection The total course contains 1 4 gm of antimony

Within the past few years Alves and Blair have successfully used a rapid method of therapy for schistosomiasis They gave 0 6 to 0 91 gm of sodium antimonyl tartrate in six doses distributed over a 36 hour interval These authors stressed the necessity of giving the injections slowly

Stibophen as a 6 3 per cent aqueous solution is given intramuscularly every second day excepting for the first three doses which are given daily For an adult the doses are successively 1 5 cc, 3 5 cc, and 5 0 cc until a total of 75 cc has been given

Mills reported good results with the use of 4 cc of lithium antimonyl thiomalate (each ml containing 10 mg of antimony) given intramuscularly 6 days weekly for 2 weeks Mills also used 5 cc of stibophen given by a similar schedule with good results

Side effects of these compounds are similar to those of the trivalent antimony compounds, mentioned above, but differ in degree, the antimonyl tartrates being more prone to provoke reactions than stibophen or lithium antimonyl thiomalate Immediate reactions are likely to be cough, nausea and vomiting, and, rarely, collapse, these reactions are much less likely to occur if the injections are made slowly During the course of therapy, vomiting, anorexia, diarrhea, weakness, excessive perspiration, loss of weight, and pain in the joints may occur Tarr, and Schroeder et al have found that electrocardiographic changes may occur without associated clinical findings referable to the heart or evidence of organic lesions The untoward symptoms clear up shortly after treatment, the electrocardiograms may become normal in a few days to 2 months

Caution must be exercised when treating patients with liver and kidney damage The liver, because of its uptake of antimony, is the organ most affected in antimony intoxication In chronic schistosomiasis, hepatitis, or cirrhosis must be presumed to be present but the treatment should be administered, except in hopeless cases to keep further

not be administered concurrently with other metallic compounds or cardiovascular depressants

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SWIMMER'S ITCH

This disease occurs in the north central states and is due to Schistosoma cercariae penetrating the skin but, because man is an accidental host, the schistosomes do not develop to maturity The cercariae probably die within the skin and release allergens, giving rise to severe itching Preliminary work by Olivier indicates that antihistaminic agents have value in relieving the distressing pruritus No individual prophylactic measures have been developed although procedures may be used about bathing areas to reduce the snail population

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TAPEWORM INFECTIONS

With few exceptions, tapeworms require two hosts to complete their life cycles As larvae, they are somatic parasites encysting in almost all tissues of the host, as adults, they live in the lumen of the intestine Tapeworms while in the intestine are relatively innocuous parasites and oral treatment is fairly effective The tissue invading tapeworm larvae that infect man however, cause serious and often fatal illnesses and no known chemotherapeutic measure is effective against these parasites

The large adult tapeworm parasites infecting man in the United States are the beef tapeworm (*Taenia saginata*) and the fish tapeworm (*Diphyllobothrium latum*) Less frequently diagnosed but actually more common is the dwarf tapeworm (*Hymenolepis nana*) A common tapeworm of dogs and cats (*Dipylidium caninum*) is sometimes found in children The pork tapeworm

(*Taenia solium*) is rare in man in the United States The pork tapeworm and the hydatid tapeworm (*Echinococcus granulosus*) will be discussed under the heading Larval Tapeworm Infections because of the pathogenicity of the larvae in man

Intestinal Tapeworm Infections The therapeutic regimen should be designed to clean the intestinal tract so that the worm will be better exposed to a high concentration of the drug None of the recommended drugs available will always be effective in removing the head of the tapeworm, although all will usually bring away long chains of segments of the parasite The head of the tapeworm is small and is often difficult to recover in the material passed following treatment, but if it is not found, re treatment should await the reappearance of segments or eggs in the stools It is recommended that the stools be examined for segments or eggs about 3 months after treatment, if the examination shows no evidence of the tapeworm the treatment may be considered successful

The depth that the tapeworm head is buried in the mucosa probably varies from time to time There is an element of chance, therefore, whether cure will result from treatment lack of success is not necessarily due to ineffectiveness of the therapeutic regimen or impotency of the drug but it may be due to the relative inaccessibility of the head to the therapeutic agent

It is wise to use saline purges and a non fatty vehicle to lessen absorption of any fat-soluble component of the drug The safety of the tapeworm anthelmintics lies only in their lack of absorption through the intestinal wall They produce less nausea and are more effective if given by a duodenal tube

Tapeworm segments are motile and it has been observed that they contract and may break apart when they strike a cold surface Better results of treatment have been observed when passages are made into warm water

The patient should be hospitalized on the day before treatment Only a light, low residue meal is given in the evening Thirty to 60 gm of magnesium sulfate, with adequate water, and an enema are given at bedtime

Breakfast is withheld on the day of treatment and another enema is given A tube is passed into the duodenum and its location is checked fluoroscopically The drug is then given in the prescribed manner Food is withheld until the bowels move copiously All movements are passed into a bedpan containing warm water

CHEMOTHERAPY The drug most commonly used is oleoresin of aspidium or male fern This drug deteriorates upon aging and should not be stored over long periods of time The adult dose should not exceed 6 cc. of the oleoresin and it is best given in di

Oleoresin of aspidium	6 cc
Powdered acacia	8 gm
Distilled water q s	60 cc

One half of this emulsion is given by a duodenal tube and the remainder is given one hour later with a saline cathartic Magnesium sulfate may be added to the emulsion Proportionately smaller doses are used for small adults and children Pregnancy and diseases of the heart, liver, and kidneys are contraindications to the use of male fern

Untoward symptoms are vomiting or those of the nervous system indicating absorption, such as headache, vertigo twitchings, and visual disturbances The advent of alarming symptoms calls for supportive treatment such as heat parenteral fluids, and procedures to hasten evacuation

Carbon tetrachloride and tetrachloroethylene in dosages as for hookworm infections have also been used with success against intestinal tapeworms Tetrachloroethylene does not cause liver damage in therapeutic doses, but it is less effective against tapeworms than carbon tetrachloride Hexylresorcinol in doses as for Ascaris infections has been used with success against intestinal tapeworms

Recently several investigators have indicated that atabrine is effective against

m.

3

tablets one hour later and a purge 3 hours later Of 30 patients treated in this manner, 25 were freed of their tapeworms (*T saginata, T solium*, and *D latum*) Several patients had reactions 2 had intense vomiting

1 had discoloration of the skin, and 1 had abdominal pain

PREVENTION OF INTESTINAL TAPEWORM INFECTIONS The beef tapeworm is acquired by the ingestion of the larvae in undercooked beef and the fish tapeworm is similarly acquired from certain fresh water fish Beef carcasses are carefully examined for tapeworm larvae at packing plants having trained inspectors, and if larvae are found, the meat is made safe for consumption before being sold However, locally butchered meat or meats from plants without adequately trained inspectors may harbor the viable larvae Meat that is shipped across state lines is federally inspected and safe from tapeworms The fish tapeworm is often acquired from eating gefullte fish, a Jewish dish containing raw fish Frequently it is acquired by housewives who taste fish foods during their preparation

The dog tapeworm is acquired by children [illegible] son to person by fecal contamination of the hands, although it is possible that a tapeworm of mice and rats is identical and the disease may be acquired from their droppings

Larval Tapeworm Infections Generally a tapeworm uses a different host for the larval and adult stages The pork tapeworm however, may develop as either a larva or adult in man A person harboring an adult pork tapeworm is endangered in that reverse peristalsis may carry the eggs from the lower intestine to the high intestine where they will hatch The embryos can penetrate the mucosa and reach the blood stream to be disseminated throughout the body In the tissues they grow to larvae about 0 5 cm in diameter, they may occur by the thousands In the brain these cysticerci manifest their presence in a variety of symptoms such as epileptiform seizures and often cause death when vital areas are involved The presence of an adult pork tapeworm in the intestine carries considerable significance and treatment should not be delayed The treatment for the adult tapeworm is the same as for the beef tapeworm There is no specific treatment for the cysticercosis caused by the disseminated larval forms Prevention of the infection is in avoidance of undercooked pork *Taenia solium* is a common parasite in many of the tropical and subtropical countries and particular care should be taken by travelers to these countries to eat only well cooked pork

The other larval tapeworm of man is a [illegible] the disease is often seen in immigrants A single egg of this species when swallowed will give rise to a hydatid cyst within which new infected forms develop as the cyst [illegible] infectious cyst fluid is allowed to get on other tissues, and if the germinal layer is not completely removed or devitalized The disease in dogs is acquired from their ingestion of carcasses of infected sheep, cattle, and hogs Prevention lies in the proper disposal of such carcasses so that dogs cannot become infected from these sources

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ASCARIASIS

In the United States infections with *Ascaris lumbricoides,* the large roundworm, are generally due to only a few worms but occasionally cases are encountered with massive infections Not infrequently, the first knowledge of the infection is obtained when a worm migrates from the rectum or is vomited The finding of eggs of Ascaris in the feces indicates the presence of at least one female worm but male worms or immature females may be present without being demonstrated by stool examination

Persons with Ascaris eggs in the feces should be treated In some cases, however, after passage of a single worm the stool examinations reveal no eggs Empirical treat-

ment is not recommended in these cases but the feces should be examined over a period of several months because of the possibility of immature worms being present when the first worm was passed

Occasionally in the United States and frequently in some other parts of the world patients will be found to harbor hundreds of ascarides *It is in these cases that* care must be exercised in selecting an anthelmintic that will rapidly paralyze or kill the ascarides rather than stimulate them because intestinal obstruction may result in the latter case (see Hookworm Therapy)

Chemotherapy The drug of choice for the treatment of ascariasis is hexylresorcinol *The drug is available in gelatin-covered pills* (caprokol pills Sharp and Dohme) containing 0 2 gm of hexylresorcinol A light meal is given on the evening preceding treatment breakfast is omitted and the full dose is given at one time The adult dose is 5 pills (1 0 gm of hexylresorcinol) with proportionately lesser doses for children to a minimum of 2 pills (0 4 gm) for children under 6 years of age Brown recommends 0 1 gm for each year of age up to 10 years Following the administration of the drug food is withheld for 4 to 5 hours A saline cathartic is given at 4 to 24 hours after therapy in order to expel the worms Patients can ordinarily remain ambulant during treatment

Hexylresorcinol pills should be swallowed without rupturing the coating otherwise burns of the oral mucosa will result The use of alcoholic beverages during therapy is contraindicated because hexylresorcinol is especially soluble in alcohol other fluids may be given freely Gastro enteritis and peptic ulcer are usually considered contraindications to therapy with hexylresorcinol

Orally administered hexylresorcinol has little toxicity Einhorn Miller and Whittier reported nausea in one of the 98 patients treated Other investigators have reported anorexia abdominal pain and diarrhea We have seen one case with "burns about the anus following therapy

Oil of chenopodium is effective against Ascaris but it is also quite toxic Its use is limited to those instances where the cost of hexylresorcinol is prohibitive Craig and Faust state that a combination of chenopodium and tetrachloroethylene (0.3 cc of oil of chenopodium and 2 7 cc of tetrachloroethylene for adults) is both safe and efficient and recommend this mixture for therapy

Obstructive symptoms from ascariasis whether ensuing spontaneously or resulting from improper treatment have been managed successfully with belladonna morphine paraffine oil and oil enemata

Ascaris eggs may be passed in the feces for several days after elimination of adult worms Brown records the passage of worms for 10 days after treatment The feces should be examined 2 weeks after treatment and the presence of eggs at that time indicates failure of therapy Craig and Faust state that *it is safe to repeat* hexylresorcinol therapy after 3 days Ascaris larvae migrating through the body will be unaffected by the treatment.

Prevention Ascaris infections are acquired by the ingestion of eggs from polluted soil The eggs require at least 9 days to become infective after they have been passed in the feces The eggs remain viable longest in a light soil in a shady place There is evidence that the ova may remain viable in such locations for several years even surviving freezing winter temperatures

The disease often occurs in cities because of dooryard pollution" where children may contaminate the soil in play areas Areas suspected of fecal contamination should be spaded up in order to decrease the chances of ingestion of the eggs Feces should be disposed of in a sanitary manner and children should be trained not to defecate where soil contamination will constitute a hazard

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ENTEROBIASIS
(Pinworm Infections)

than

dren among whom Cram claims that as many as 50 per cent have been found to be infected in some studies The pinworm has a peculiar life cycle in that the gravid female crawls out of the anus deposits up to 10 000 eggs on the perianal region and dies Jones and Jacobs report that eggs become infective in about 6 hours and may live for several weeks depending on such factors as temperature and humidity According to Nolan and Reardon the eggs become distributed throughout the household even being carried about by air currents Thus despite the usual sanitary precautions the eggs can reach the mouth of the host Hatching occurs in the upper part of the gastro intestinal tract and development takes place in the intestine There is no multiplication the intensity of the infection depends upon the number of eggs ingested

Two important considerations are frequently overlooked in treating cases for pinworm infection First pinworm infection is often familial Generally all members of a household except small infants are infected some continuously and some intermittently Therefore the treatment of one member who is known to have the disease is only temporarily successful because he may be reinfected following the migration of a worm from a lightly infected individual For this reason it is recommended that all household members over one year of age be treated simultaneously in spite of lack of evidence that they are infected The second important consideration is that treatment must be extended over an interval long enough to allow eggs in the household to become noninfectious before the completion of therapy A 23 day interval has been sufficient in our experience to accomplish this objective

Wright and R[illegible]

[illegible] (Lilly) will prevent staining from the dye and probably lessens the gastro intestinal irritation The tablets are available in 3/10 and ½ grain sizes A useful rule in calculating dosage is to give one tablet of the 3/10 grain size daily for each year of apparent age or one tablet of the ½ grain size daily for each 3 years of apparent age The maximum dose per day is six ½ grain tablets for adolescents and adults The tablets are given before meals the total number of tablets to be given each day is divided into two or three doses Thus for adults 2 of the larger tablets are given before each meal

The schedule of therapy calls for two courses of 8 days separated by a 7 day interval Therefore the treatment takes 23 days

Patients should be warned not to chew the gentian violet tablets because of the [illegible]

usual side effects are due to local irritation These effects are nausea vomiting abdominal pain and diarrhea With advent of these symptoms the dosage can be reduced to about two thirds of the prescribed amount and therapy continued Sometimes it may be necessary to discontinue the gentian violet for several days and then to continue with the smaller doses In such cases it is wise to continue the gentian violet over a longer interval until the total prescribed amount is taken Uncommonly vertigo and lassitude occur presumably from absorption Serious organic disease of the liver and kidneys have been considered contraindications to gentian violet therapy Alcoholic drinks are forbidden lest they increase the absorption of gentian violet

The treatment of small children who cannot swallow the tablets is not satisfactory If the child cannot be trained to take the tablets without crushing them in the mouth it is necessary to resort to the use of enemas for therapy Enemas probably act by mechanically flushing out the more mature worms and it is doubtful that the addition of medicaments has any advantage over saline enemas Whatever enema is used it should be given nightly at the hour of sleep for the same 23 day interval that the remainder of the household is taking gentian violet

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die undisturbed

Phenothiazine has been used for treatment of pinworm infections by a number of investigators with success equal to that of gentian violet Phenothiazine has the dis

ment is not recommended in these cases but the feces should be examined over a period of several months, because of the possibility of immature worms being present when the first worm was passed

Occasionally in the United States, and frequently in some other parts of the world, patients will be found to harbor hundreds of ascarides It is in these cases that care must be exercised in selecting an anthelmintic that will rapidly paralyze or kill the ascarides rather than stimulate them, because intestinal obstruction may result in the latter case (see Hookworm Therapy)

Chemotherapy The drug of choice for the treatment of ascariasis is hexylresorcinol The drug is available in gelatin covered pills (caprokol pills, Sharp and Dohme) containing 0 2 gm of hexylresorcinol A light meal is given on the evening preceding treatment, breakfast is omitted, and the full dose is given at one time The adult dose is 5 pills (1 0 gm of hexylresorcinol) with proportionately lesser doses for children to a minimum of 2 pills (0 4 gm) for children under 6 years of age Brown recommends 0 1 gm for each year of age up to 10 years Following the administration of the drug, food is withheld for 4 to 5 hours A saline cathartic is given at 4 to 24 hours after therapy in order to expel the worms Patients can ordinarily remain ambulant during treatment

Hexylresorcinol pills should be swallowed without rupturing the coating, otherwise "burns" of the oral mucosa will result The use of alcoholic beverages during therapy is contraindicated because hexylresorcinol is especially soluble in alcohol, other fluids may be given freely Gastro enteritis and peptic ulcer are usually considered contraindications to therapy with hexylresorcinol

Orally administered hexylresorcinol has little toxicity Einhorn, Miller, and Whittier reported nausea in one of the 98 patients treated Other investigators have reported anorexia, abdominal pain, and diarrhea We ...e seen one case with "burns" about the ...following therapy

...of chenopodium is effective against but it is also quite toxic Its use is ...ed to those instances where the cost of ...lresorcinol is prohibitive Craig and ...st state that a combination of chenopodium and tetrachloroethylene (0 3 cc of oil of chenopodium and 2 7 cc of tetrachloroethylene for adults) is both safe and efficient, and recommend this mixture for therapy

Obstructive symptoms from ascariasis, whether ensuing spontaneously or resulting from improper treatment, have been managed successfully with belladonna, morphine, paraffine oil, and oil enemata

Ascaris eggs may be passed in the feces for several days after elimination of adult worms Brown records the passage of worms for 10 days after treatment The feces should be examined 2 weeks after treatment and the presence of eggs at that time indicates failure of therapy Craig and Faust state that it is safe to repeat hexylresorcinol therapy after 3 days Ascaris larvae migrating through the body will be unaffected by the treatment

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The disease often occurs in cities because of "dooryard pollution" where children may contaminate the soil in play areas Area suspected of fecal contamination should be spaded up in order to decrease the chance of ingestion of the eggs Feces should be disposed of in a sanitary manner and children should be trained not to defecate where soil contamination will constitute a hazard

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ENTEROBIASIS

(Pinworm Infections)

Pinworm infections are more common than is generally realized Usually the highest incidence is encountered in school-age chil

dren among whom Cram claims that as many as 50 per cent have been found to be infected in some studies The pinworm has a peculiar life cycle in that the gravid female crawls out of the anus deposits up to 10 000 eggs on the perianal region and dies Jones and Jacobs report that eggs become infective in about 6 hours and may live for several weeks depending on such factors as temperature and humidity According to Nolan and Reardon the eggs become distributed throughout the household even being carried about by air currents Thus despite the usual sanitary precautions the eggs can reach the mouth of the host Hatching occurs in the upper part of the gastro intestinal tract and development takes place in the intestine There is no multiplication the intensity of the infection depends upon the number of eggs ingested

Two important considerations are frequently overlooked in treating cases for pinworm infection First pinworm infection is often familial Generally all members of a household except small infants are infected some continuously and some intermittently Therefore the treatment of one member who is known to have the disease is only temporarily successful because he may be reinfected following the migration of a worm from a lightly infected individual For this reason it is recommended that all household members over one year of age be treated simultaneously in spite of lack of evidence that they are infected The second important consideration is that treatment must be extended over an interval long enough to allow eggs in the household to become noninfectious before the completion of therapy A 23 day interval has been sufficient in our experience to accomplish this objective

Wright and Brady recommend as the drug of choice gentian violet given orally The use of a coating such as the enseals coating (Lilly) will prevent staining from the dye and probably lessens the gastro intestinal irritation The tablets are available in 1/6 and ½ grain sizes A useful rule in calculating dosage is to give one tablet of the 1/6 grain size daily for each year of apparent age or one tablet of the ½ grain size daily for each 3 years of apparent age The maximum dose per day is six ½ grain tablets for adolescents and adults The tablets are given before meals the total number of tablets to be given each day is divided into two or three doses Thus for adults 2 of the larger tablets are given before each meal

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usual side effects are due to local irritation These effects are nausea vomiting abdominal pain and diarrhea With advent of these symptoms the dosage can be reduced to about two thirds of the prescribed amount and therapy continued Sometimes it may be necessary to discontinue the gentian violet for several days and then to continue with the smaller doses In such cases it is wise to continue the gentian violet over a longer interval until the total prescribed amount is taken Uncommonly vertigo and lassitude occur presumably from absorption Serious organic disease of the liver and kidneys have been considered contraindications to gentian violet therapy Alcoholic drinks are forbidden lest they increase the absorption of gentian violet

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There is little evidence that hygienic measures alone can control pinworm infections. It may even be possible that vigorous house cleaning *stirs* up ova that would otherwise die undisturbed

Phenothiazine *has been used for treatment* of pinworm infections by a number of investigators with success equal to that of gentian violet. Phenothiazine has the ex-

advantage that it is more toxic than gentian violet, and may cause hemolytic anemia Toxic effects may persist after withdrawal of the drug Its general use is not recommended at this time

PREVENTION The usual method of introduction of pinworms into a household is unknown but because of the greater incidence in preschool and school age children these groups are probably responsible for its introduction Presumably small children in close contact in play and sleep acquire the infection from one another Adults are likely to lose their infections spontaneously unless in household contact with infected children Cases should be treated play habits conducive to transmission should be altered and bad hygienic practices such as biting the fingernails should be discouraged

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TRICHINOSIS

If it were possible to establish the diagnosis of trichinosis early in the disease the elimination of some worms from the intestine by frequent saline purges might result at least in a lessening of the severity of the acute period However trichinosis cannot be diag l at this time except under unusual umstances No specific drug has been d to be effective against the worms in intestinal mucosa or against the circulating and tissue invading larvae Treatment in the acute episode has been found to be merely palliative

Prevention Trichinosis results from the ingestion of viable larvae in meat from hogs bear, or certain other mammals Because the infection is acquired from meat herbivorous animals do not become infected in nature Pork is the usual source of the infection for man it is important therefore to cook or prepare pork products so that any larvae present will be killed Under Federal meat inspection regulations any pork customarily eaten without further preparation by the housewife is processed to kill larvae and is safe Such preparations not coming under the jurisdiction of the Federal system may or may not be so processed dependent on state and local regulations Pork should be cooked so well that all parts of the meat reach a temperature of 130° F a temperature that will change the color of the meat from red to gray The practice of raising swine on

disease from the country

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ANCYLOSTOMIASIS
(Hookworm Infections)

There are two species of hookworm that mature in man *Necator americanus* and *Ancylostoma duodenale* The latter is often called the Old World hookworm and it is not known to be endemic in the United States although it is being found in veterans who acquired it during World War II *A duodenale* is more pathogenic and less amenable to treatment than *N americanus* A differentiation cannot be made by the ova but must be made by examination of the adults

As with other intestinal parasitic infections attention must be given to emptying the gastro intestinal tract before administering the specific therapy Saline purges are used because of the solubility of the anthelmintics in oily substances On the evening before treatment a light meal is given followed by an enema or saline purge The drug is administered on the next morning without breakfast although fluids are allowed Another saline purge is given with the anthelmintic or following the drug

The safety of the drugs used against hookworms is dependent on their lack of

solubility in water and their inability to be absorbed through the intestinal wall

Drugs TETRACHLOROETHYLENE Tetrachloroethylene is the drug of choice for the treatment of hookworm infections The patient should be hospitalized on the evening

0 1 to 0 2 cc for each year of apparent age

Side effects such as drowsiness vertigo and vomiting may occur with treatment Alarming drowsiness is combated by hastening evacuation of the tetrachloroethylene with saline cathartics and enemas

Liver disease is considered to be a contraindication to tetrachloroethylene although liver damage has not been reported from the use of therapeutic doses Other contraindications are gastro enteritis alcoholism severe malnutrition severe anemia and a history of having had treatment with heavy metals such as arsenic and mercury The presence of Ascaris ova in the feces is a contraindication to tetrachloroethylene therapy because ascarides stimulated by the drug may cause intestinal obstruction if enough are present

Tetrachloroethylene is effective in removing hookworms but the treatment often has to be repeated to remove all *A duodenale* present In many veterans several courses of treatment were necessary to remove all of the worms present in one series only 55 per cent were freed of ova in the feces after two treatments Treatment with tetrachloroethylene should not be repeated within 10 days

Tetrachloroethylene is available in capsules from several drug firms Broken capsules should be discarded

Occasionally patients are treated en masse for hookworms Liquid medicinal tetrachloroethylene may be used the drug being dispensed directly into the dose of magnesium citrate by pipette Because tetrachloroethylene may oxidize to phosgene on exposure to air bottled tetrachloroethylene should be shaken with sodium bicarbonate solution in a separatory funnel before use The phosgene will be removed with the aqueous phase

HEXYLRESORCINOL Patients may be treated with hexylresorcinol without hospitalization The drug is administered as for Ascaris infections The drug will remove only about one half to two thirds of the hookworms present and for that reason it is less desirable than tetrachloroethylene Some worms will not be removed and the only criterion for effectiveness in light infections is by the use of quantitative egg counts such as the Stoll count performed before and after treatment

OTHER CHEMOTHERAPEUTIC AGENTS Sometimes because of the lack of availability of tetrachloroethylene and hexylresorcinol other drugs must be used for treatment These drugs have less of a margin of safety and are not generally recommended They are given in divided doses after preparation of the patient Thymol has been used for many years and has been given in doses of 4 gm for adults Oil of chenopodium has had a wide acceptance and is given in a dose of 1 to 2 cc Carbon tetrachloride was the precursor of tetrachloroethylene for hookworm therapy and is equally effective but considerably more toxic the usual dose is 3 cc for adults

Severe Hookworm Disease The severity of hookworm disease is roughly proportional to the number of hookworms present Thus with only a few worms no clinical manifestations of the disease will be evident In heavy hookworm infestation the manifestations may be associated with severe anemia severe malnutrition weakness and apathy Such cases are poor risks for anthelmintic therapy Effort should be made to correct the anemia and malnutrition The patient is put to bed and given a balanced diet supplemented with vitamins and massive doses of iron Transfusions may be necessary After the patient has improved with this regimen specific anthelmintic therapy ca be given Hexylresorcinol is recommend for the first treatment in these cases

Creeping Eruption In addition to two species of hookworms mentioned man is also subject to transient infection hookworms of dogs and cats

Ancylostoma braziliense of the southern states In the skin these larvae produce "creeping eruption and they may even play a role in the production of Loffler s syndrome These larvae in the skin produce tortuous elevated linear lesions that are intensely pruritic The larvae move a few millimeters to a few centimeters each day and remain alive for several months Freezing the area with ethyl chloride or solid carbon dioxide has given the most consistent beneficial results Fuadin (see Schistosomiasis) has been claimed to be beneficial but Dolce and Franklin observed *improvement in only* 3 of 14 patients

Prevention Hookworms are acquired by contact with soil previously contaminated with the eggs The eggs hatch and the larvae develop to the infectious stage in a few days these larvae are motile and can even climb up on moist blades of grass The larvae penetrate the skin on contact and after a complex migration through the tissues reach the intestinal lumen Therapy is directed against the adults in the intestine, no drug is known to be effective against the mi*grating forms of the hookworm in humans* The eggs and larvae survive best in moist shady places where the soil is a sandy loam

Preventive measures include the therapy of known cases and the avoidance of soils that might be contaminated Shoes should be worn in suspected areas Promiscuous defecation is an important factor in maintaining the infection in the soil Prevention in endemic areas is also a sanitation problem for public health agencies Education of school children as to the dangers of hookworm dis*ease and how to prevent it is valuable At tempts may be made to alter the habits of* natives who perpetuate the disease The best permanent measure lies in the installation of safe privies or sewer systems and teaching the residents to use these facilities The use of human excrement for fertilizer, as is practiced in many countries needing a rigid economy is a source of hookworm infection for which no satisfactory control measure has been found at the present time

"Creeping eruption" is acquired in areas where infected dogs and cats have defecated These places may be under sheds in the *woods and* frequently on beaches Where the disease exists dogs should be frequently treated for hookworm *infections* avoidance of contact of skin with soils that might be infected is recommended

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FILARIASIS

(Bancroft s Filariasis)

Two filarial parasites of man *Wuchereria bancrofti* and *Wuchereria malayi* cause similar clinical manifestations The disease is called filariasis or better Bancroft s filaria*sis The disease can be classified into three* clinical types (1) cases with microfilariae in the peripheral circulation but without symptoms (2) cases with intermittent acute symptoms such as lymphadenitis and lymphangitis with or without microfilariae in the blood and (3) cases with late sequelae such as chyluria or elephantiasis with or without microfilariae The available evidence indicates that the microfilariae play no part in the production of symptoms the manifestations are due to the presence of adult *worms* and *in some cases* to concomitant bacterial *infection*

The objectives of therapy must be under

[illegible] Three

of microfilariae has been used as the criterion of efficacy of chemotherapeutic agents Within recent years several drugs have been *shown to eliminate microfilariae.* Adequate time has not elapsed to determine the effects of these drugs on adult worms and on the symptoms

Three types of compounds have been shown to eliminate microfilariae in Bancroft s

filariasis These are antimonials arsenicals and one recently tested piperazine derivative hetrazan (Lederle) The effects of these compounds on adult worms are known only by inference because of the difficulty in recovering mature worms Scanty evidence is available indicating that the compounds alleviate the acute attacks of filariasis

Chemotherapy Although antimonials given parenterally have been used for many years in the experimental therapy of filariasis only in recent years has their action been unequivocally demonstrated Brown used a trivalent antimony compound (anthiomaline Merck) and found that the number of microfilariae was rapidly reduced during treatment and that they even disappeared from the blood in several cases Culbertson Rose and Oliver Gonzalez used a pentavalent compound (neostibosan Winthrop) which caused a slow drop in the numbers of microfilariae and in a year s interval about half of their treated patients were microfilaria free Both groups of investigators had inferential evidence that the adults were affected by the treatment and subsequently antimony compounds have been shown to affect the adults of a filarial parasite of dogs In general the reactions with anthiomaline were more severe than reactions to neostibosan

Thetford Otto Brown and Maren reported their results with the use of a phenyl arsineoxide (arsenamide) administered intravenously in 6 cases showing microfilariae There was a rather prompt reduction or disappearance of the microfilariae noted at the end of treatment Reactions to the drug were mild The authors believe that the adult worms were affected on the basis of febrile reactions and eosinophilia during treatment and local reactions in 2 patients probably at the site of adult worms

Santiago Stevenson Oliver Gonzalez and Hewitt treated 26 cases with hetrazan (1 diethylcarbamyl-4 methyl piperazine hydrochloride) This organic compound was effective in reducing the number of microfilariae within one day when given orally in doses of 0 5 to 2 mg per kilogram of body weight three times daily Observations made up to 5 months after treatment showed reduced numbers of microfilariae in all patients and some were freed of circulating microfilariae Reactions to the drug were mild with fever leukocytosis and eosinophilia in most patients Four patients had a localized lymphadenitis that the authors attributed to injury to adult worms

It may be said that three different types of drugs are known to affect the microfilariae and there is indirect evidence that all have an effect on the adult worms The value of these drugs for relief of symptoms is not entirely clear Thetford et al cite the case of a patient with scrotal swelling hydrocele enlargement of femoral and inguinal nodes and brawny edema of the right leg These symptoms were presumably due to filariasis although microfilariae were not observed

dent No report has indicated that the use of the drugs mentioned above has any unfavorable effect upon the disease by accelerating the development of sequelae

It is considered advisable to use a microfilaricidal drug in case of filariasis both because of a possible favorable effect on the symptoms and because of the reduction of numbers of microfilariae with decreased danger of mosquito transmission Of the drugs that have this action hetrazan is safest and easiest to administer

Other than the somewhat empirical use of a drug the treatment of the acute episodes of lymphangitis and lymphadenitis and of the subacute and chronic sequelae is palliative In cases in which secondary bacterial invasion may be present penicillin or sulfa drugs should be given Plastic operations have been developed for treating elephantiasis they are most successful in scrotal elephantiasis

Prevention The disease can be prevented either by avoidance of the bites of the mosquito vector or by reducing the microfilaria level in the human hosts The vectors of filariasis breed and remain close to human habitations Hence an infected individual may serve as the reservoir from which he himself is repeatedly reinfected It is important therefore to the patient as well as to his neighbors that the microfilariae be eliminated Thus the measures used for other mosquito transmitted diseases are applicable such as sleeping under bed nets, DDT spray

ing and eradication of mosquito breeding places Large scale treatment of microfilaria carriers probably will result in decreased chances of infection if carried out over a period of time

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FILARIASES OTHER THAN BANCROFT'S FILARIASIS

In addition to human infections with filaria of the genus *Wuchereria* infections occur with *Onchocerca volvulus*, *Loa loa*, *Mansonella ozzardi*, and *Acanthocheilonema perstans* Because the latter two parasites are non pathogenic, they will not be discussed

Onchocerciasis Onchocerciasis differs from the other human filariases in that the microfilariae are found in the skin, and the adults are localized in subcutaneous nodules The late sequela of blindness is probably due to cumulative injury from microfilariae in the eye, the adults cause no other symptom than the production of nodules

Until 1947, the only treatment was the surgical removal of nodules with the hope that the numbers of microfilariae would be decreased In 1947, Van Hoof, Henrard Peel, and Wanson showed that suramin (Bayer 205 or naphuride sodium, Winthrop) eliminated the microfilariae and killed the adult Onchocerca Mazzotti and Hewitt in 1948 reported that hetrazan (Lederle) reduced the numbers of microfilariae Further observations on the use of both drugs were made by Burch

Suramin is administered intravenously at weekly intervals in 1 gm doses for adults for 8 weeks The optimal dosage for hetrazan is not established, Burch used up to a total of 46 mg per kilogram of body weight over a 3 week interval The drug is given orally in two or three daily doses

Burning of the feet was the only important reaction attributed to the suramin per se and no reaction was attributed to hetrazan With either drug however, severe reactions sometimes occurred, apparently due to the tissue reaction from dead and dying microfilariae These reactions were mainly ocular, as photophobia, lacrimation, burning and itching, and skin reactions such as pruritus induration, and edema In general, hetrazan produced more severe side effects than suramin but with both drugs the severity was correlated with the degree of the infection The reactions from hetrazan ensued promptly after a single dose of the drug, the reactions from suramin came on more gradually after four to six injections

ie in less

irs in Africa and in limited areas in Central America The disease is transmitted by small biting gnats Protection is based on the use of insect repellents applied to the skin, pyrethrum sprays for quick "knock down," and application of DDT to surfaces where the insects may rest Large scale eradication of breeding places has not been practical, in spite of the fact that larval stages of the insect are susceptible to the action of DDT

Loaiasis Adult *Loa loa* migrate through the subcutaneous tissue, and their migrations are probably related to a syndrome called Calabar swelling, similar to angioneurotic edema The adult worms sometimes may be seen migrating across the eye beneath the conjunctiva The microfilariae are found in the blood and probably are innocuous

The adult worms may be removed surgically while migrating across the eye Preliminary reports indicate that hetrazan may be effective against the microfilariae

PREVENTION Loaiasis occurs in Africa and it is not uncommon in returned missionaries The disease is transmitted by a biting fly about the size of the housefly and is related to deer flies The insects usually bite out doors during daylight hours Presumably, the use of newer repellents on the skin will deter them from biting

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GUINEA WORM INFECTION

The female guinea worm (*Dracunculus medinensis*) when mature is about 1 meter in length It is observed clinically as a long tortuous elevation of the skin, usually of the lower extremities, generally superficial, particularly over bony prominences The male worms probably lie deep in the tissues and are not demonstrated clinically

When the female has matured, it migrates to the skin and the head of the fully developed female worm becomes located under a blister that forms on the skin This blister ruptures when it comes in contact with water, thereby liberating embryos The live worm in situ produces little reaction unless there is secondary infection or rupture or death of the worm These complications may cause considerable disability owing to inflammation and scarring, sometimes interfering with locomotion by involvement of muscles, tendons, or joints Treatment is directed at the removal of the female worm

The treatment of antiquity was slowly delivering the worm from the tissues by rolling a short length daily onto a split stick until it is completely removed Medical science has improved considerably on the treatment of the ancients with a similar method After the blister is formed, the area is exposed to fresh water in a basin and the developed embryos escape Using an aseptic technic, the head is exposed and secured to the skin and a dressing applied Each day thereafter, the delivered part of the worm is again exposed to fresh water to empty the uterus

gentle traction can be exerted on the worm lest it be broken within the tissues, giving rise to complications Other disadvantages of this method are that considerable time is required (since the adult female is about 1 meter in length and only 1 or 2 cm can be delivered daily) and secondary bacterial infection may occur

Operative removal is sometimes under-

ing the extraction

Elliott has described a method using intramuscular injections of an oily emulsion of phenothiazine near the site of the worm He injects as much as 4 gm of phenothiazine at one sitting, and gives injections at weekly intervals At 5 to 7 days after the first injection, extraction is started and as much as 1 foot of the worm may be removed at once Even if no worm is presenting the induration resolves and the sinuses dry in 10 to 14 days

Prevention Important foci of the disease exist in Asia and Africa, but there are also a few small foci in Central and South America Infestation has been reported only in animals within the United States The disease is acquired from drinking water containing Cyclops infected with the parasite Cyclops are removed from our waters by sand filtration, and chlorine presumably kills larvae and adults, so that little danger of human infection exists where water supplies meet our present-day standards

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REFERENCE

Elliott, M New Treatment for Dracontiasis *Tr Roy Soc Trop Med & Hyg*, 35 291, 1942

CHAPTER III

DISEASES OF METABOLISM

DIABETES MELLITUS

Four different sets of conditions should be recognized in the treatment of proved diabetes mellitus They are

(1) Mild diabetes manageable by restriction of food
(2) Severe forms of the disease requiring adjunctive use of insulin routinely
(3) Acidosis and other acute complications such as infection and surgical or traumatic events
(4) Chronic complications particularly those of vascular origin

Each of these requires specific methods of treatment suitable for the class and varying only in detail The first three demand regulation of the disordered state of carbohydrate metabolism With proper understanding effective control of them can be accomplished with diet alone diet together with insulin or insulin together with supplementary measures In the fourth class regulation of the carbohydrate metabolism is advisable but often ineffective Other medical measures are required but even so progress of the complication often cannot be stopped

Criteria for Good Control Most authorities agree that it is desirable to control abnormal hyperglycemia and glycosuria so far as possible without unendurable inconvenience to the patient and danger of severe shock from insulin In some instances these two qualifications make it advisable to permit minimal or transient glycosuria as the lesser of two evils But with proper care the majority of diabetic patients can be maintained in approximately normal sugar balance without either of these penalties This should be done whenever possible The necessity for condoning some glycosuria in certain cases should not be permitted to encourage laxity of control in the majority Established criteria for good routine management consists of the maintenance of normal nutrition and as good control of abnormal blood and urine sugar as possible without more serious penalties The following description of therapeutic methods is based on this principle

Mild Diabetes Dietary Control. Probably about half of all proved uncomplicated cases of diabetes mellitus can be managed by restriction of the food intake These patients usually are obese in middle or advanced age not diabetic for long and have not suffered from the disease They do not show excessively high sugar levels and develop acidosis only when acute complications exist They have never used insulin or have used it only temporarily When these characteristics are present an effort to manage the diabetes by diet should always be made and will often be successful Loss of excess weight is usually advisable in addition Diet restriction therefore is doubly important. The use of insulin may prevent loss of weight by encouraging greater food consumption

Three types of diet are suitable for this class of patients The last two are also appropriate for maintenance of normal nutrition even though insulin is required

Desugarizing When abnormal glycosuria and hyperglycemia exist when the patient uses no insulin and when no acute infection or ketonuria is present desugarization by diet is indicated

A desugarizing diet is one which will support normal weight at minimum activity will maintain protein balance will not cause ketonuria and will supply adequate accessory elements such as bulk minerals vitamins and water It must be as low as possible in glucose value without conflicting with those requirements (If body weight is excessive it may also be restricted in calories below a maintenance level by reduction of its fat content In that case the total calories required for maintenance must be calculated according to the methods described below with subsequent arbitrary reduction of the fat This insures freedom from ketosis)

Calories From 20 to 35 calories per kilogram of body weight per day are required for maintenance of weight at minimum activity * Older and inactive persons require less, young and active persons more An average allowance for an older individual weighing 140 lbs would be 63 kg × 25 calories or 1575 calories per day

Protein About 1 gm of protein per kilogram of body weight per day is ordinarily adequate to preserve nitrogen balance and other needs for protein in adults * The average person selected above would therefore, need about 63 gm of protein daily This would yield 252 calories daily Deducted from the total caloric requirement (1575 − 252), this leaves 1323 calories to be supplied by carbohydrates and fat

Carbohydrate Fat Ratio When the fat supply is much more than double the carbohydrate, ketosis is likely to occur Yet the carbohydrate must be as low as possible without ketosis, in order to accomplish desugarization Ratios of about 1 2 in grams ($2C = F$) are most desirable in desugarizing diets In the example given above, 1323 calories must come from carbohydrates and fat, or $4C + 9F = 1323$ If $2C = F$, $4C = 2F$. Therefore, $2F + 9F = 1323$ and $F = 120$ By selection the carbohydrate is one half the fat, in this case 60

The fuel values for this desugarizing diet are thus C − 60, P − 63, F − 120, G − 109, Calories 1572 Children and people of greater or lesser weights and degrees of activity can be supplied by similar simple calculations

Food Prescription Table I gives this example of a desugarizing diet in detail For obvious reasons, bread and other starchy foods should be omitted from the selection The form employed shows the percentage composition of the common foods used It includes the calculations involved in supplying the required fuel values Table II shows the choice of individual foods from each group Better training is provided and greater accuracy insured if the patient is re-

* Children require as much as double these amounts

TABLE I

DESUGARIZING DIET *

Standard Foods		*Grams of Foods Permitted at Each Meal*			*Daily Totals—Fuel Values*			
See Groups for Selection	G	Morning	Noon	Night	24 Hours	C	F	P 0
Vegetable	4		200	200	400	16	4	0
Fruit	8	100		100	200	16	2	
Bread	58							
Meat	16		50	50	100	0	25	15
Eggs	4	2			2	0	12	12
Milk	7	100	100	100	300	15	9	12
Cream	9	100	100	100	300	15	9	60
Butter	9	10	10	10	30	0	.3	25 5
G Per Meal		34	34	42	Total	62	61	124
Height		66'	4 x C		243	1 x C	62	
Weight		140	4 x P		244	0 58 x P	35 4	
Ideal Weight		140	9 x F		1116	0 10 x F	12 4	
Calorie Requirement		1575	Calories		1603	Glucose	110	

* See footnote, Table II

TABLE II

STANDARD FOOD GROUPS *

Foods listed in groups below may be selected in any combination according to amounts specified in diet requisition			
Vegetable (Fresh cooked or canned without added sugar)	Asparagus Celery Lettuce Endive Chard Watercress Radishes Pickles	Cauliflower Cabbage Sauerkraut Brussels Sprouts Summer Squash Artichokes Okra Eggplant	String Beans Wax Beans Cucumbers Tomato Spinach Beet Greens Broccoli Onion
Fruit (Fresh cooked or canned without added sugar)	Oranges Grapefruit Lemons Limes	Strawberries Canteloupe Honeydew Watermelon	Canned Fruits (4 10% C) Gingerale
Bread (Weigh before toasting)	White Rye Whole Wheat	Corn Bread Graham Bran Bread	Rolls (Plain) Biscuits Buns
Meat (Free from excess fat Weigh after cooking)	Beef Lamb Mutton Veal Pork Ham Bologna Frankfurters	Chicken Turkey Duck Goose Tongue Liver Sweetbreads Kidney	Fish Lobster Crabmeat Shrimps Scallops Cottage Cheese
Milk	Whole Milk		
Cream	20 per cent Cream Sour Cream		Olives Avocados
Butter (and other fats)	Butter Oleomargarine Meat Fat Cod Liver Oil		French Dressing Mayonnaise Salad Oil

* Reprinted from *Diabetes Mellitus in General Practice* by Arthur R Colwell 1947 (courtesy of The Year Book Publishers 304 S Dearborn St Chicago)

quired to weigh the diet for a practice period at least rather than use household measures *When this is impossible* the diet may be transposed into estimated portions by reference to Table III

The variety afforded by the substitution list shown in Table IV is sufficiently desirable to warrant the use of food scales and the metric system

Additions When a desugarizing diet is in effect the elevated blood and urinary sugar may either disappear or level off above normal In the former case cautious additions should be made, preferably in the form of carbohydrate foods, for greater palatability, to provide more calories for greater activity and to reduce the chances of ketosis in case of unavoidable glycosuria Additions that can be made without return of abnormal blood and urinary sugar levels are advantageous If sugar reappears the need for insulin is established Methods for using it will be considered in a subsequent section Additions to the food supply can be made after desugarization by insulin

Maintenance When desugarization has been accomplished, either by diet or by the adjunctive use of insulin, a diet is required which is capable of supporting normal weight and health at the optimal activity

TABLE III

APPROXIMATE WEIGHT IN GRAMS OF COMMON PORTIONS OF FOOD *

Vegetables

200 gm

1 Glass Juice
1 Head Lettuce Endive
1 Bowl Soup
1 Large Tomato

100 gm

1 Sauce dish Cooked Vegetable
1 Small Tomato
10 Brussels Sprouts
1 Small Glass Juice

50 gm

5 Radishes
3 Stalks Celery
4 Small Pickles
1 Medium Dill Pickle

Fruits

200 gm

1 Glass Juice
1 Large Apple

100 gm

1 Saucedish Cooked Fruit
½ Medium Grapefruit or Melon
1 Large Peach
1 Medium Apple or Orange
½ Large or 1 Small Banana
3 Halves Cooked Apricot

50 gm

1½ Slices Pineapple
½ Cup Berries
3 Prunes
15 Grapes

Cooked Cereals and Starches

100 gm

½ Cup Gruel or Porridge
½ Cup Cooked Rice or Cereal
½ Cup Macaroni or Spaghetti
2 6" Ears Corn
1 Medium Potato
½ Cup Mashed Potato
1 Saucedish Cooked Vegetable

50 gm

1 Small Potato
½ Medium Sweet Potato

Breads and Flour Products

50 gm

1 Large Roll or Muffin
1 6" Waffle
1 4" Pancake
1 Doughnut

20 gm

1 Slice Bread
1 Small Roll
4 Soda Crackers
2 Rye Krisp
8 10 Potato Chips

Meats and Cheese

200 gm

1 Large Steak

100 gm

½ Broiled Chicken
1 Medium Hamburger
2 Frankfurters
½ Cup Salmon
5 Oysters
4 Tbsp Cottage Cheese

50 gm

2 Small Lamb Chops
1 Loin Pork Chop
1 Slice Bologna
10 Shrimps
½ Pkg Cream Cheese
1 Thick Slice Cheese

Milk Cream and Fats

200 gm

1 Glass Milk or Cream

100 gm

1 Small Glass Milk or Cream
½ Cup Ice Cream

20 gm

2 Tbsp Cream
2 Links Pork Sausage
4 Strips Bacon
1 Tbsp Peanut Butter

10 gm

1 Pat Butter
1 Tbsp Salad Dressing
6-10 Shelled Nuts
2-3 Olives

* See footnote Table II

TABLE IV

SUBSTITUTION FOOD GROUPS *

Standard Foods in these amounts	May be exchanged for other foods in these amounts			
100 gm *Vegetable*	Carrots Beets Turnips Rutabagas Standard Fruits	50 gm Mushrooms Peppers Pumpkin Kohlrabi		30 gm Peas Parsnips Catsup Horseradish
100 gm *Fruit*	Apples Pears Peaches Apricots	60 gm Raspberries Blackberries Blueberries Loganberries	Cherries Pineapple Canned Fruit (11 15% C)	40 gm Bananas Plums Grapes Prunes Cooked Figs Fresh
20 gm *Bread*	60 gm (cooked wt) Corn Potato Baked Squash Baked Beans Lima Beans Macaroni Spaghetti Noodles	35 gm (cooked wt) Baked Potato Sweet Potato	Rice Barley Oatmeal Cornmeal Flour Farina Hominy Popcorn	15 gm (dry wt) Corn Flakes Wheat Flakes Rice Flakes Shredded Wheat Cream of Wheat Pretzels Crackers Rye Krisp
25 gm *Meat*	50 gm Oysters Clams Frog Legs Milk Buttermilk	20 gm Cheese American Brick Swiss Cream		One Egg
One *Egg*	50 gm Oysters Clams Frog Legs Milk Buttermilk	25 gm Meat Poultry Fish Liver Tongue	Lobster Shrimp Crabmeat Scallops Cottage Cheese	20 gm Cheese American Brick Swiss Cream
50 gm *Milk*	50 gm Buttermilk Skim Milk	25 gm Evaporated Milk		10 gm Condensed Milk Cocoa (dry wt)
50 gm *Cream*	25 gm Cocoanut (fresh) Whipping Cream	15 gm Shelled Nuts Peanut Butter Shredded Cocoanut		10 gm Bitter Chocolate
10 gm *Butter*	20 gm (cooked wt) Bacon Pork Sausage	50 gm Cream = 50 gm Milk and 8 gm Butter		

* See footnote, Table II

required by the patient This must be as convenient and palatable as possible within the limitations imposed by the necessity for controlling the sugar balance and maintaining uniformity and accuracy of treatment Conservative rules for the selection of such a diet may be outlined as follows

Calories Age and activity are the most important factors governing the selection of a maintenance diet Adults usually require from 25 to 40 calories per kilogram per day Lower amounts are needed by older and sedentary persons and more by the young and active Heavy manual laborers and children may demand as many as 50 calories per kilogram Thin people and men need more, women and obese persons less An average allowance for a young 160 lb adult would be 75 kg × 35 calories or 2520 calories

Protein At least 1 gm of protein per kilogram per day is necessary for maintenance of normal nutrition There is seldom any harm in giving more Children need fully

360 calories, leaving 2160 to be supplied by carbohydrate and fat

Carbohydrate Fat Ratio Ratios of less th
k
ir
ing more generous amounts of carbohydrates are more difficult to balance with or without insulin They are, therefore not used by the author except when special indications exist

Conservatism dictates that a ratio of 1 1 to 3 2 in carbohydrates to fat in grams is most desirable In the example chosen above a r
rie
4C
4F
2160, F = 166 and C also is 166, since by selection, it is equal to F

A maintenance diet for this person, therefore, contains fuel values of C – 166 P – 90 and F – 166, G – 235, Calories 2518 It should be noted that the glucose value of this diet is more than double that of the desugarizing diet selected in the previous section, because of its higher ratio and the greater size and activity of the patient for whom it was planned

Food Prescription Table V gives the detailed kinds and amounts of common foods used in the fulfillment of these fuel requirements and their distribution into meals Tables II, III, and IV provide data making it possible to enjoy variety of selection and to avoid weighing foods, if desired, by conversion of the diet into measured equivalents

Weight Reduction Either the desugarizing type of diet or the maintenance diet can be modified for purposes of reducing weight when required

Reducing diets are planned in exactly the same manner as described for desugarization and maintenance but the fat content is decreased arbitrarily after planning the food values to a level which will impose a caloric deficit This forces the combustion of stored fats in amounts which approximate the deficit, and preserves the total exogenous and endogenous fat combustion at the level and ratio planned originally, thereby insuring freedom from ketosis

In the example of a maintenance diet described in the preceding section arbitrary reduction of the fat from 166 gm to 40 gm

imposed because the total calories are reduced from 2520 needed for maintenance to 1384 Restrictions of the carbohydrate could impose a greater deficit and more rapid weight reduction although only about 330 additional calories could be eliminated in this way (without creating ketogenic conditions by lowering the ratio to less than 1 2)

When the patient is overweight the diet should be planned as if the excess weight were to be maintained and the fat reduced secondarily This avoids prescription of diets which are accidentally ketogenic or submaintenance in protein When the patient is underweight or normal the diet should be planned to maintain the ideal weight, because excess calories and protein can do no harm

Insulin Requirements When dietary adjustment fails to produce good control of abnormal glycosuria and hyperglycemia without nutritional penalties, the routine use of insulin becomes necessary The need for it

TABLE V

MAINTENANCE DIET *

Standard Foods		*Grams of Foods Permitted at Each Meal*				*Daily Totals–Fuel Values*			
See Groups for Selection	G	Morning	Noon	Night	10 P M	24 Hours	C	P	F
Vegetable	4		200	200		400	16	4	0
Fruit	8	150	150	150		450	36	4 5	0
Bread	58	40	40	40	40	160	84 8	14 4	3 2
Meat	16		50	100		150	0	37 5	22 5
Eggs	4	2				2	0	12	12
Milk	7		200		100	300	15	9	12
Cream	9	100		100	100	300	15	9	60
Butter	9	20	20	20	5	65	0	6	55 3
G Per Meal		55	69	72	40	Total	167	91	165

Height	70	4 x C	668	1 x C	167
Weight	160	4 x P	364	0 58 x P	52 8
Ideal Weight	160	9 x F	1485	0 10 x F	16 5
Caloric Requirement	2520	Calories	2517	Glucose	236

* See footnote Table II

usually is permanent although borderline cases in which its temporary use permits good control later without it are not infrequent On this account insulin should always be urged rather than to allow even minimal hyperglycemia There are more important considerations than freedom from diabetic symptoms chiefly those of islet damage and danger of infectious and vascular complications from persistent hyperglycemia

ACTION OF INSULIN AND ITS MODIFICATIONS To understand the proper use of various in [illegible] monly used modifications is essential

All insulin preparations are virtually ineffective when given by any other route than parenterally They are almost always given hypodermically Each patient must be instructed in the technic of the hypodermic injection Figure 1 shows the method of administration taught by the writer A 1 cc syringe graduated into tenths and a 27 gauge ½ in stainless steel needle are preferred

Unmodified Insulin Regular insulin (solution of amorphous insulin) and crystalline insulin (solution of zinc insulin crystals) are almost identical in action The effects of single large doses on glycemia and glycosuria are shown in Fig 2 in contrast with those of the most commonly used depot preparation protamine zinc insulin Their action is prompt reaching a peak in about 4 hours intense and fairly brief exhausting their effect in about 12 hours For these reasons these unmodified preparations are most useful in emergencies and to supplement the depot insulins In routine treatment they must be injected more than once daily (sometimes every 6 hours or so) in order to provide overlapping effect For routine use they have been largely replaced by depot insulins with more sustained less intense action

Because their absorption rates do not de

pend on any depot principle the unmodified insulins are more uniform and dependable in effect than the longer acting preparations This is decidedly advantageous in the extremely severe labile forms of diabetes seen chiefly among children and young adults where minor variations in the intensity of insulin effect often result in gross changes toward hypoglycemia or hyperglycemia

Protamine Zinc Insulin This is the most commonly used depot preparation It is a suspension of amorphous crystals of insulin precipitated in combination with a mono protamine (salmine) and zinc in a neutral aqueous vehicle Correct dosages are obtained only by thorough mixing of the suspension in its vehicle After hypodermic injection insulin is released from its slowly soluble combination with the protamine and zinc probably by enzymatic action This is the "depot" effect

Gradual weak and prolonged reduction

yond 24 hours daily injections overlap each other in effect with the result that the response to any given daily dosage is not seen for several days Accordingly the response to changes or omission of its daily administration is not seen for days for the same reason

Protamine zinc insulin is most useful in less severe forms of diabetes in which details of insulin timing are relatively unimportant and weak insulin effect is all that is required This may be true even when large daily doses are required owing to "insulin insensitivity" or relative refractoriness for any reason

Insulins with Intermediate Action During recent years some refinements in effective insulin therapy have become possible as a result of the development of insulin modifications with time action intermediate between those of unmodified insulin and the original depot preparation protamine zinc insulin Neither the fast nor the slow acting standard insulin fits the needs of the patient with severe diabetes very well Ordinary insulin must be injected several times daily Even then its effect wanes so rapidly in severe diabetes that hyperglycemia and glycosuria occur during the hours of sleep even without food At the other extreme protamine zinc insulin is so weak and prolonged in effect that dosages sufficiently large to control the glycosuria which follows the meals are likely to cause severe insulin shock during hours of fasting especially during sleep In the past it has often been supplemented by separate injections of regular insulin for this reason Small amounts of regular insulin added to larger amounts of protamine zinc insulin are precipitated by the excess protamine present and lose their identity

Globin insulin with zinc is the only intermediate insulin sold at the present time It is an acid aqueous solution of insulin in combination with beef globin and zinc It is partially precipitated after injection hence it has both a rapid and sustained effect It is more rapid and less prolonged in action than protamine zinc insulin but less rapid and intense and decidedly more prolonged in action than unmodified insulin The average response to a single large dose is shown in Fig 3 in comparison with two commonly used protamine insulin mixtures In Fig 2 contrasts of its effects with those of similar single doses of ordinary and protamine zinc insulin are demonstrated

Protamine insulin mixtures containing excesses of unmodified insulin also possess time action of an intermediate character Thorough mixtures containing about twice as much regular or crystalline as protamine zinc insulin fit the needs of most severe diabetic patients Occasionally the mixtures must contain three times as much regular insulin as protamine zinc insulin for best results There is not much difference in the responses to single doses of globin insulin and a 2 1 mixture Probably the latter preparation permits greater overlapping of depot effect in single daily dosage A 3 1 mixture is decidedly more intense and less prolonged than either of the others The mixtures are compared graphically in Fig 3 in contrast with the fast and slow effects of ordinary and protamine insulin shown in Fig 2

These intermediate insulins are most appropriate when diabetes is so severe that (1) fasting glycosuria and hyperglycemia follow the use of ordinary insulin (2) postcibal glycosuria occurs with amounts of protamine insulin sufficiently large to control fasting hyperglycemia (3) nocturnal hypo-

Fig 1 Technic of insulin injection (see footnote Table II)

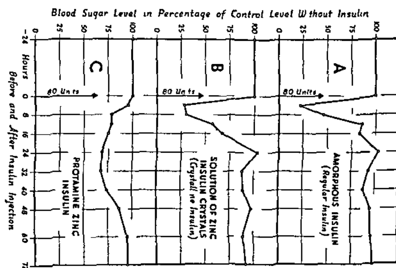


Fig 2 Action curves of large single doses of standard insulins (see footnote Table II)

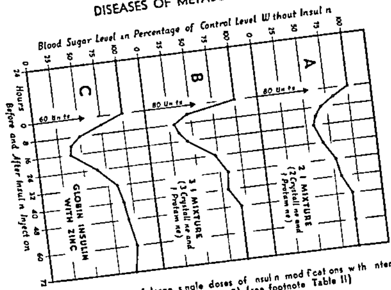


Fig 3 Action curves of large single doses of insulin modifications with intermediate timing (compare with Fig 2) (see footnote Table II)

glycemia and insulin shock are caused by amounts of protamine zinc insulin large enough to control glycosuria following meals They are almost always used in single daily doses before breakfast in the morning

There is not much choice between globin insulin and insulin mixtures The chief advantage of the former is the fact that it can be used as marketed The mixtures must be prepared in the ampule or syringe from market supplies of their component parts They possess the advantage of greater elasticity for individual needs by change in proportions Greater overlapping of effect from the 2 1 mixture is also desirable in some patients The choice between them depends on their appropriateness as determined by actual trial and comparison in individual patients

A suspension of protamine insulin crystals containing about 40 per cent as much protamine as standard protamine zinc insulin ("NPH50") possesses time activity comparable to those of the 2 1 mixture and globin insulin with zinc

Insulin in Severe Diabetes As indicated above diabetes is not infrequently so severe that rapid shifts in sugar balance occur with insulin preparations which do not efficiently fit the feeding and fasting needs of the patient About one-half of all insulin treated patients fall into this category Diabetes ... existed for a long time or which has developed early in life almost always behaves this way Special insulin technics are then required for best results Selection of the most appropriate insulin often makes the difference between good health and some degree of disability

The most common pattern in diabetes of this type is as follows Without insulin glycosuria is intense symptoms severe and acidosis extremely likely to occur With ordinary insulin daily multiple injections are required for good control including one during the normal hours of sleep Fasting hyperglycemia is high unless a substantial dose of one of the depot insulins is used or ordinary insulin is given during the night Protamine insulin in dosage great enough to reduce the early morning sugar level to normal permits heavy glycosuria to follow meals and yet is likely to cause nocturnal hypoglycemia The insulin requirement commonly ranges from 40 to 80 units daily although exceptions may occur in insulin sensitive individuals

Diabetes so severe that these characteristics are present requires one of the depot insulins with intermediate action Globin insulin or one of the protamine insulin mixtures containing at best twice as much insulin as protamine insulin often corrects the faults in the timing of the standard preparations

Globin insulin may stop both the postprandial glycosuria and nocturnal hypoglycemia and yet preserve an approximatel

normal fasting level It may cause insulin reactions at the time of its peak action (8 to 16 hours after injection) or permit slightly high early morning levels, owing to inadequate overlapping In that event the slightly less intense, more prolonged action of a 2 1 mixture is preferable

INSULIN IN DIABETES OF MODERATE SEVERITY When reduction of the food supply fails to control abnormal glycosuria and hyperglycemia and yet diabetes is judged not to be severe, moderate doses of protamine zinc insulin are preferred Daily injections before breakfast are given

Dosages required usually range from about 10 to 40 units daily Much more may be required by insensitive patients even when their diabetes is inherently not severe

When the diet has been set at a maintenance level which is not extravagant in carbohydrate and blood and urine sugar levels are persistently high a daily trial dose of protamine zinc insulin should be injected, preferably for about one week, and the response observed The fasting blood sugar concentration before breakfast measures this response most specifically because it determines the peak action of the depot effect and warns of impending hypoglycemia Postprandial and 24 hour glycosuria should also be observed because they may indicate the need for one of the intermediate depot insulins

Adjustment of the dosage of protamine zinc insulin should be made (ordinarily at intervals of not less than 3 or 4 days) until the early morning blood sugar level is approximately normal If no glycosuria then occurs at any time of day, the balance may be considered satisfactory Gradually progressive lowering of the fasting sugar level may then follow, owing to slowly accumulating depot effects, exercise, or improvement in severity of the diabetic process This requires subsequent reduction in dosage and may allow withdrawal of all insulin and satisfactory control by diet alone

If any glycosuria follows meals in spite of the attainment of normal or subnormal fasting sugar levels with protamine zinc insulin, redistribution of the food or insulin is necessary When the disproportion between the day and night sugar levels is not great, correction of both is sometimes possible by transfer of carbohydrate foods from meal time to a lunch at bedtime The total carbohydrate of the diet can be reduced with the same result, along with a reduction in the size of the dose of protamine zinc insulin

When the amount of glycosuria following meals is great or the nocturnal hypoglycemia severe, protamine zinc insulin should be discontinued and one of the intermediate depot preparations substituted

On the other hand, if either of these insulins permits afternoon or evening glycosuria to occur in spite of daily doses large enough to reduce nocturnal glycemia to normal, an insulin with even more rapid action is required A mixture containing two and one half or even three times as much regular insulin as protamine insulin is then needed Diabetes of this type is unusual

INSULIN IN LABILE ("BRITTLE") DIABETES A good many young (and some older) patients with diabetes of long standing exhibit a pattern which defies almost all attempts at perfect control of glycosuria without insulin shock On ordinary programs of management they behave unpredictably A constant diet and insulin regimen permit sudden and unexpected shifts in glycemia from one extreme to the other for no apparent reason These patients accept large waves of glycosuria alternating with severe insulin reactions with resignation and concern Their number is increasing because of the lengthened life and greater duration of diabetes of young people with the disease

A satisfactory balance is difficult to secure for these patients and sometimes impossible Ordinarily some degree of glycosuria must be accepted as the lesser of two evils the other being frequent insulin shock Compromise with ordinary standards of control is inevitable in some cases The most satisfactory criteria for treatment involve (1) maintenance of normal nutrition, (2) freedom from diabetic symptoms and all ketonuria, (3) elimination of severe reactions from insulin (4) as little glycosuria as possible without great inconvenience in the diet or insulin routine

With presently available methods of treatment two specific plans are most satisfactory Both take advantage of the fact that insulin modifications with sustained action are unpredictable in their intensity of overlapping

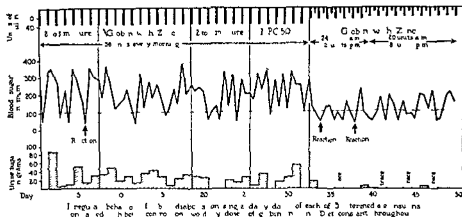


Fig 4 Irregular behavior of labile diabetes with one dose daily of various intermediate insulins Improved control when one of them was given twice daily (see footnote Table II)

effect Modifications with more rapid action injected more frequently distribute their available insulin more uniformly and efficiently

The most effective but also most inconvenient of these plans involves the injection of unmodified insulin three or four times daily including an injection during the hours of sleep Four doses of equal size given at approximately 6 hour intervals along with feedings of equal value are capable of yielding good control even in the most difficult patients of this type (The fact that this is possible appears to prove that the unpredictable behavior is due to inconstant rates of insulin release inherent in all depot insulins given at longer intervals) The regimen is so arduous that few patients can adhere to it for long The two nighttime doses may be replaced by one dose of an intermediate preparation with less inconvenience but also with less consistent control

The most satisfactory plan (which compromises between convenience and perfect control) involves the use of one of the intermediate insulins twice daily Figure 4 shows the improved control secured in one brittle case when this technic was substituted for one larger dose given once daily

Specifically the method requires that the total daily insulin dose be divided into a larger dose (two thirds to three-quarters of the total) before breakfast and a smaller dose (from one third to one quarter of the total) at bedtime along with a small lunch

Shifts in balance are minimized by this method Slightly smaller amounts of insulin are needed probably because of greater efficiency The exact timing of the insulin is not important provided one of the intermediate modifications is used The effect of the morning dose is judged by the sugar levels in the late afternoon and evening that of the night dose by the levels before and after breakfast Redistribution of food improves the results after uniform patterns of

insulin effect exceeds the available supply of sugar for any reason signs of insulin shock appear In diabetes this happens most frequently when dosage is too high or distributed improperly when absorption of depot insulin is accelerated (as by accidental injection into a vein) when diabetes is improved after injection or as a result of treatment or when food is delayed reduced or vomited It also occurs commonly when exercise improves sugar utilization or accelerates release of insulin from injection depots It is always annoying sometimes alarming and rarely fatal In moderate severity it may lead to mental irresponsibility and physical inco-ordination simulating drunkenness and thus be the cause of violent accidents especially in driving an automobile

TIME. Each type of insulin has its own characteristic time for insulin shock to result

normal fasting level It may cause insulin reactions at the time of its peak action (8 to 16 hours after injection) or permit slightly high early morning levels, owing to inadequate overlapping In that event the slightly less intense, more prolonged action of a 2 1 mixture is preferable

INSULIN IN DIABETES OF MODERATE SEVERITY When reduction of the food supply fails to control abnormal glycosuria and hyperglycemia and yet diabetes is judged not to be severe, moderate doses of protamine zinc insulin are preferred Daily injections before breakfast are given

Dosages required usually range from about 10 to 40 units daily Much more may be required by "insensitive" patients even when their diabetes is inherently not severe

When the diet has been set at a maintenance level which is not extravagant in carbohydrate and blood and urine sugar levels are persistently high, a daily trial dose of protamine zinc insulin should be injected, preferably for about one week, and the response observed The fasting blood sugar concentration before breakfast measures this response most specifically, because it determines the peak action of the depot effect and warns of impending hypoglycemia Postprandial and 24 hour glycosuria should also be observed because they may indicate the need for one of the intermediate depot insulins

Adjustment of the dosage of protamine zinc insulin should be made (ordinarily at intervals of not less than 3 or 4 days) until the early morning blood sugar level is approximately normal If no glycosuria then occurs at any time of day, the balance may be considered satisfactory Gradually progressive lowering of the fasting sugar level may then follow, owing to slowly accumulating depot effects exercise or improvement in severity of the diabetic process This requires subsequent reduction in dosage and may allow withdrawal of all insulin and satisfactory control by diet alone

If any glycosuria follows meals in spite of the attainment of normal or subnormal fasting sugar levels with protamine zinc insulin, redistribution of the food or insulin is necessary When the disproportion between the day and night sugar levels is not great, correction of both is sometimes possible by transfer of carbohydrate foods from meal time to a lunch at bedtime The total carbohydrate of the diet can be reduced with the same result, along with a reduction in the size of the dose of protamine zinc insulin

When the amount of glycosuria following meals is great or the nocturnal hypoglycemia severe, protamine zinc insulin should be discontinued and one of the intermediate depot preparations substituted

On the other hand, if either of these insulins permits afternoon or evening glycosuria to occur in spite of daily doses large enough to reduce nocturnal glycemia to normal, an insulin with even more rapid action is required A mixture containing two and one half or even three times as much regular insulin as protamine insulin is then needed Diabetes of this type is unusual

INSULIN IN LABILE ("BRITTLE") DIABETES A good many young (and some older) patients with diabetes of long standing exhibit a pattern which defies almost all attempts at perfect control of glycosuria without insulin shock On ordinary programs of management they behave unpredictably A constant diet and insulin regimen permit sudden and unexpected shifts in glycemia from one extreme to the other for no apparent reason These patients accept large waves of glycosuria alternating with severe insulin reactions with resignation and concern Their number is increasing because of the lengthened life and greater duration of diabetes of young people with the disease

A satisfactory balance is difficult to secure for these patients and sometimes impossible Ordinarily some degree of glycosuria must be accepted as the lesser of two evils the other being frequent insulin shock Compromise with ordinary standards of control is inevitable in some cases The most satisfactory criteria for treatment involve (1) maintenance of normal nutrition (2) freedom from diabetic symptoms and all ketonuria, (3) elimination of severe reactions from insulin (4) as little glycosuria as possible without great inconvenience in the diet or insulin routine

With presently available methods of treatment two specific plans are most satisfactory Both take advantage of the fact that insulin modifications with sustained action are unpredictable in their intensity of overlapping

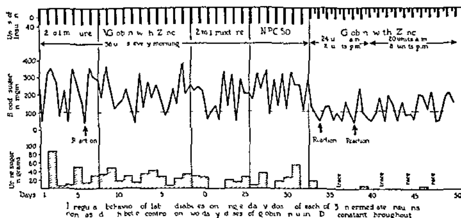


Fig 4 Irregular behavior of labile diabetes with one dose daily of various intermediate insulins Improved control when one of them was given twice daily (see footnote Table II)

effect Modifications with more rapid action injected more frequently distribute their available insulin more uniformly and efficiently

The most effective but also most inconvenient of these plans involves the injection of unmodified insulin three or four times daily including an injection during the hours of sleep Four doses of equal size given at approximately 6 hour intervals along with feedings of equal value are capable of yielding good control even in the most difficult patients of this type (The fact that this is possible appears to prove that the unpredictable behavior is due to inconstant rates of insulin release inherent in all depot insulins given at longer intervals) The regimen is so arduous that few patients can adhere to it for long The two nighttime doses may be replaced by one dose of an intermediate preparation with less inconvenience but also with less consistent control

The most satisfactory plan (which compromises between convenience and perfect control) involves the use of one of the intermediate insulins twice daily Figure 4 shows the improved control secured in one brittle case when this technic was substituted for one larger dose given once daily

Specifically the method requires that the total daily insulin dose be divided into a larger dose (two thirds to three-quarters of the total) before breakfast and a smaller dose (from one third to one-quarter of the total) at bedtime along with a small lunch Shifts in balance are minimized by this method Slightly smaller amounts of insulin are needed probably because of greater efficiency The exact timing of the insulin is not important provided one of the intermediate modifications is used The effect of the morning dose is judged by the sugar levels in the late afternoon and evening that of the night dose by the levels before and after breakfast Redistribution of food improves the results after uniform patterns of

insulin effect exceeds the available supply of sugar for any reason signs of insulin shock appear In diabetes this happens most frequently when dosage is too high or distributed improperly when absorption of depot insulin is accelerated (as by accidental injection into a vein) when diabetes is improved after injection or as a result of treatment or when food is delayed reduced or vomited It also occurs commonly when exercise improves sugar utilization or accelerates release of insulin from injection depots It is always annoying sometimes alarming and rarely fatal In moderate severity it may lead to mental irresponsibility and physical inco-ordination simulating drunkenness and thus be the cause of violent accidents especially in driving an automobile

TIME. Each type of insulin has its own characteristic time for insulin shock to result

Unmodified insulin causes shock about 3 to *5 hours after injection* intermediate preparations such as globin insulin and protamine insulin mixtures in about 8 to 16 hours and protamine insulin *during the longest period* of fasting usually during the night With any type of insulin exercise increases the chances of shock especially during the late afternoon Reactions seldom occur within 2 or 3 hours immediately following the ingestion of food These rules of timing frequently are useful in distinguishing insulin reactions from other suspicious phenomena

Symptoms In its mildest form insulin shock is characterized by hunger weakness and trembling Children are unaccountably fretful Unreasonable behavior and failure to *recognize the cause of the symptoms are* common In a more advanced stage there is gray pallor profuse perspiration inco ordination and silly or sullen behavior Diplopia and numbness of the tongue or lips may be present In this stage physical accidents may occur owing to poor judgment and inco ordination Alcoholic intoxication may be suspected The most severe stage resembles an epileptic seizure Unconsciousness rigidity and convulsions are characteristic The patient is usually in a cold sweat breathing is stertorous and efforts to arouse him are *unsuccessful Labile diabetes may pass into* this stage with no warning Sleeping subjects may be discovered in that condition probably because earlier symptoms were unrecognized during sleep

When unconsciousness due to insulin shock has persisted a long time residual mental and physical symptoms may continue even after normal sugar levels have been restored Prolonged stupor is the ordinary residue but abnormal *personality changes* motor signs and even psychotic behavior may occur These sequelae are probably due *to cerebral damage* When they occur they are confusing because the usual favorable response to administered sugar is masked thus raising doubt about the diagnosis

Diagnosis Severe insulin shock is easily distinguished from diabetic coma by its rapid onset absence of air hunger ordinarily sugar free and *ketone free urine low blood* sugar and normal plasma carbon dioxide combining power It is not so easy to dis*tinguish* from head injury, apoplexy, epilepsy and myocardial infarction with unconsciousness due to shock Blood sugar analysis settles the diagnosis if quickly available If not and even though the urine con*tains sugar* intravenous injection of glucose is indicated immediately for differentiation Usually failure to improve promptly rules out insulin shock *if sufficient glucose is given*

Treatment Treatment consists of giving enough sugar to stop the symptoms and signs In mild reactions this can be accomplished by feeding fruit juice sugar candy or milk until recovery is complete Ten to 20 gm of carbohydrate are practically always sufficient even in severe shock During unconsciousness swallowing may be impaired and oral feedings aspirated into the respira*tory system It should be tested with small* amounts of water and food withheld if doubtful Epinephrine hypodermically followed by sugar by mouth or glucose by vein in 10 to 20 gm amounts are then preferred and rapidly effective

Although it is not possible to avoid insulin reactions in any patient who uses the hormone most of them can be prevented by the consistent application of a few simple rules The patient must eat his prescribed *food on* time not increase insulin unless it is indicated unequivocally take extra carbohydrate *during unaccustomed exercise* and not ignore mild symptoms of hypoglycemia With depot insulins occasional fasting blood sugar estimations warn when dosage is excessive The physician must know how the effect of depot preparations is distributed respect their cumulative effect when used initially watch for signs of improving tolerance *dur*ing effective treatment and after complications and adjust the food intake in such a *manner that* the danger of hypoglycemia is [illegible] d Most important when instability [illegible] ost pre [illegible] choice must be made between the two evils of inter [illegible]

be condoned in minimal amounts [illegible] necessary to avoid insulin shock

Acute Complications The most effective [illegible] ng acute

haste is essential Acute illness puts sugar metabolism out of control this in turn, aggravates the illness, which again affects the diabetes adversely The vicious cycle thus initiated by acute disease cannot ordinarily

frequent intervals must be applied

Acute diseases which frequently demand vigorous treatment by quickly effective methods are acidosis acute infection, surgical interference, and trauma All of these except severe forms of acidosis can be managed easily by a rational method of using ordinary insulin The treatment of precomatose and comatose states will be considered separately

Six Hour Emergency Management When heavy glycosuria with or without ketonuria, exists as a result of any acute illness, it can be eliminated within 24 hours as a rule, by judicious adjunctive use of ordi

tions It may be used in mild acidosis without symptoms during acute infection if the sugar balance is disturbed before surgery if quick control is essential, and after operations, anesthesia or severe injury which

about 6 hours after each of these feedings, (3) injections of unmodified insulin every 6 hours, after each test and before each next feeding the size of each dose determined by the response to the previous injection Figure 5 outlines the methods in diagrammatic form

Feedings In order that the supply of sugar may be constant and therefore, ignored as a possible variable affecting the sugar balance, a meal, series of feedings, or parenteral injection of uniform glucose value is given every 6 hours throughout each 24 hour period For adults, feedings of 40 gm of glucose value are most convenient Table VI lists a variety of them This value may be lowered or raised, if desired, for any given patient, but it should be maintained at a uniform level, both day and night, after it is selected in any one case, unless insulin shock demands extra sugar temporarily

TABLE VI

Parenteral and Oral Feedings Each of 40 Gm Glucose Value, for Use Every Six Hours in Emergency Management *

800 cc	5 per cent glucose	400 cc	10 per cent glucose
800 cc.	5 per cent amino acids in 5 per cent glucose	400 cc	orange or grapefruit juice
600 gm	milk	250 gm	milk
		250 gm	cream
2	eggs	40 gm	bread
200 gm	milk	10 gm	butter
200 gm	cream	200 gm	milk
30 gm	crackers or dry cereal	1	egg
100 gm	milk	40 gm	bread
100 gm	cream	150 gm	milk
150 gm	fruit †	150 gm	fruit †
15 gm	dry cereal	1	egg
100 gm	cream	40 gm	bread
100 gm	milk	10 gm	butter
100 gm	fruit †	50 gm	meat or cheese
2	eggs	20 gm	bread
20 gm	bacon	10 gm	butter
40 gm	bread	150 gm	fruit †
5 gm	butter	100 gm	cream
100 gm	meat	100 gm	vegetable †
200 gm	vegetable †	20 gm	bread
20 gm	bread	10 gm	butter or dressing
10 gm	bread or dressing	100 gm	milk
50 gm	cream	100 gm	cream
		100 gm	fruit †

* See footnote Table II

† Selected from "Standard Food Groups" shown in Table II

The alimentary capacity of the patient naturally determines the choice of individual feedings During vomiting and immediately preoperat

they should be injected at slow rates which will not flood the tissues and

transient waves of glycosuria Five per cent solutions given at rates of 2 to 3 cc per minute will not do this Sick persons with anorexia can be given liquid feedings in divided doses at rates which will supply uniform amounts of sugar every 6 hours With normal appetites the entire feeding can be taken in a substantial meal every 6 hours except during the night when a single liquid feeding is preferable

Tests About 6 hours after the beginning of each feeding period the urine is tested for sugar Greatest accuracy in judging the need for insulin results from tests of small specimens obtained shortly after previous emptying of the bladder near the end of the period Bladder retention must be avoided. The urine is tested immediately by any qualitative method by the patient attendant, or nurse The result determines the size of the next dose of insulin Blood sugar analysis is unnecessary and not expedient because of time limitations In retrospect it aids in decisions about insulin particularly when excessive but it is not indispensable for effective results

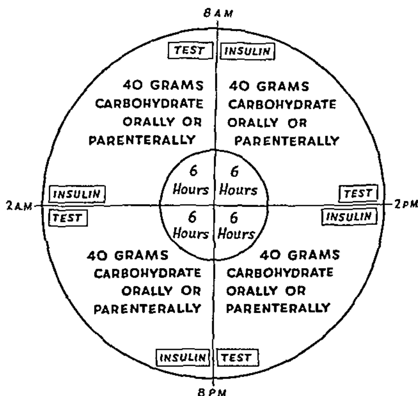


Fig 5 Six hour emergency program (Woodyatt) (see footnote Table II)

Insulin Unmodified (regular or crystalline) insulin must be used exclusively for quick regulation The size of the initial dose is determined by the severity of the diabetes previous use of depot insulins average daily requirement of the patient and intensity of the complicating illness Ordinarily from 10 to 20 units are given initially except in severe ess or resistant cases when 40 units or ore can be used safely

The effect of the initial dose and each subsequent one can be judged by the test on urine secreted 4 to 6 hours after injection If the test is heavy a substantial *increase* should be made in the next dose If the sugar clears rapidly as a result of the previous injection the dose should be *repeated or lowered* slightly If hypoglycemia results the dose should be reduced decisively The size of repeated doses is adjusted *according to* these rules until an amount is determined by trial and error, which when given re

dose can then be given, along with the uniform feedings, as long as the complication exists. Minor adjustments can be made as the insulin requirement changes.

The success of this method of using insulin depends on a number of factors. The sugar supply must be uniform day and night. Trial and error determine the insulin needed by each patient. The 6 hour interval must be maintained continuously for feedings, tests and insulin. No single dose of insulin can be omitted even if no food is taken without affecting the reliability of the method, because serious dislocation of overlapping effects thereby is introduced. Finally, depot insulins should not be adjusted while this method is in operation. If used previously

not be started until the daily requirement of the patient can be estimated and routine management begun. Their adjustment during emergencies introduces a variable which only makes decisions regarding the 6 hour dosage of supplementary insulin more difficult.

Transfer to Routine Management. Ordinary methods of diet and insulin adjustment as outlined in previous sections can be resumed whenever conditions permit. Before this is done a stable insulin requirement is desirable. The complicating illness should have subsided and the patient's appetite returned to normal.

This conversion can be made by omitting the fourth 6 hour feeding during the night, giving the entire diet in the other three meals (at mealtime instead of 6 hour intervals) and one dose of one of the depot insulins every morning before breakfast. Its size should be a little less than the sum of the 6 hour doses plus any depot insulin used previously. When no depot insulin has been used during the emergency, the regular insulin should be tapered off during the first 2 or 3 days in which the full daily dose of depot insulin is used. Stopping it suddenly

daily depots before effective insulin can be relied upon.

ADVANCED DIABETIC ACIDOSIS (PRECOMATOSE AND COMATOSE STATES). It must be appreciated that the therapeutic methods described in this section are applicable only when ketogenic acidosis exists in an advanced stage. Undoubtedly the most serious emergency caused by diabetes mellitus and usually dramatically responsive to proper treatment, the severe form of acidosis ac

ous section. Unconsciousness in diabetes caused by complications other than acidosis (*viz.*, cerebral and cardiovascular accidents, trauma, insulin shock, alcohol) should be distinguished carefully from diabetic coma and precoma and treated by appropriate methods. Strenuous therapy, as used for severe acidosis, can be disastrous if applied in mild acidosis or other forms of coma not due to acid intoxication.

In the order of their greatest importance, the useful therapeutic weapons are unmodified insulin in large doses at frequent intervals, parenteral fluids, glucose, salt replacement, and plasma and circulatory stimulants on occasion.

Insulin. Only unmodified insulin should be used. Depot insulins serve no useful purpose in the emergency, although there is some advantage in not stopping them if used previously. Ordinary insulin must be given without delay in large doses at intervals of not more than 6 hours. The prompt administration of a decisively large dose often is of lifesaving importance because time runs out. Other agents used in treatment are of no importance if too little insulin is used too late, or if effective insulin is allowed to fade by long intervals between doses.

The size of the initial dosage depends on the size and condition of the patient. In adults with vomiting, moderate breathlessness, drowsiness, and alkali reserve readings in the vicinity of 20 to 30 volumes per cent, an initial dose of 40 to 60 units is indicated. Twice as much should be given initially if extreme air hunger and deep stupor are present and the blood pressure, pulse, and

urine output are not critically affected True coma usually does not exist up to this stage After circulatory collapse has begun with cyanosis, coldness, rapid pulse, low blood pressure, oliguria or anuria, and failing respiration, all treatment is usually ineffective unless several hundred units are given immediately, at least half by vein and circulatory efficiency is restored by other supportive measures In children this suggested dosage scale should be revised according to body weight If severe infection accompanies advanced acidosis, dosages should be at least doubled

The only dependable rule dictates that *enough insulin should be given to stop the progress of the acid intoxication* without causing violent insulin shock! Ordinary doses are ineffective and massive doses not to be feared if the patient is critically ill Insulin shock can be prevented by glucose administration as required, therefore, it is better to err by giving too much rather than too little

The patient's response to the insulin given initially determines the size of subsequent dosage! If irreversible parenchymatous damage has not occurred, effective insulin is indicated primarily by improvement in respiratory distress in 3 to 5 hours Abrupt decreases in preceding diuresis and high sugar levels give confirmatory proof of adequate insulin and warn of danger of hypoglycemia These usually occur later and are of less value as early guides than the rate and depth of breathing If no improvement is seen within the first 3 to 5 hours, the initial dosage must be considered ineffective and larger amounts given promptly and watched as before A single large dose is more rapidly effective and more easily evaluated than multiple small doses at short intervals Under no circumstances should more than 6 hours elapse before additional insulin is given even after massive initial amounts with favorable response

After improvement occurs an injection of insulin should be given every 6 hours day and night, according to the principles outlined previously for the 6 hour emergency method A massive dose can be repeated, if seen to be effective, unless excessive polyuria, glycosuria and ketonuria have been [illegible]d Thereafter it can be halved every 6 hours, provided increasing glycosuria does not recur, until ordinary maintenance doses of 50 to 100 units daily (12 to 24 units every 6 hours) prevent excessive glycosuria without causing hypoglycemia Routine feeding and depot insulin control can then be resumed, as previously described Patients who have come out of severe acidosis seldom can be maintained on less than 40 units of insulin daily They usually require more

Fluids Because of vomiting and diuresis extreme dehydration always exists in advanced diabetic acidosis Its correction is secondary in importance only to sufficient insulin

During the first day of treatment at least 3 liters of water must be given to the adult of average size Four to 6 liters are probably better, although cardiac and gastric dilatation can occur readily by administration rates which are too rapid

If anuria exists fluids should be given as 5 per cent glucose to protect against insulin shock from large doses If the urinary output is satisfactory, ⅙ molar sodium lactate or normal salt (without glucose) can be used as long as heavy glycosuria is known to exist by frequent testing of catheterized specimens Delay in giving glucose helps to rehydrate the subject more rapidly because glycosuria and diuresis, which are excessive at first, are not increased by glucose which is wasted Abrupt fall in urinary volume or sugar demands prompt use of glucose solutions to prevent insulin shock

Not enough fluid can be given in early stages by routes other than parenteral ones because of vomiting and stupor

Glucose After heavy glycosuria and polyuria decrease as a result of insulin glucose with or without amino acids should be given in solution parenterally until food and fluids can be taken by mouth About 40 gm every 6 hours represents a useful and convenient rate It can be increased temporarily if hypoglycemia threatens It is highly desirable to give enough to reproduce glycosuria when the urine clears suddenly owing to large amounts of insulin The 40 gm per 6 hour rate can then be resumed when a [illegible] approached [illegible] f [illegible] feedings from Table VI

Salt Replacement Vomiting and diuresis result in significant losses of mineral elements from the body which must be replaced Sodium phosphorus and potassium have been shown to be of greatest importance in this respect

Sodium should be given in 20 to 40 gm amounts parenterally during the first day as normal saline or 1/6 molar sodium lactate solution About 2 gm of potassium should be given in addition if any signs of hypopotassemia exist (extreme muscular weakness respiratory embarrassment low blood potassium level) Phosphates are excreted in large amounts in acidosis and are necessary for normal sugar utilization Probably they should be given routinely along with sodium and water

Circulatory Support When diabetic subjects in acidosis are first seen late in the course of the acid poisoning an unavoidably high mortality rate is inevitable Characteristics of this terminal stage are cyanosis hypotension rapid thready pulse coldness anuria shallow respiration and plasma carbon dioxide combining power below 10 volumes per cent Recovery from this condition is possible only if the shock like state can be restored toward normal even though all other methods of treatment are carried out with meticulous thoroughness

Two or 3 units of blood plasma given intravenously may restore adequate circulation Other fluids in large amounts are indispensable External heat should be used Circulatory stimulants such as caffeine camphor and even digitalis sometimes appear to help Epinephrine should not be used. If the circulation cannot be improved by these or other methods the outcome is usually fatal In borderline situations in which it can the use of those methods along with heroic treatment of the acidosis represents the difference between success and failure of treatment

Chronic Complications Treatment dur [illegible]

when the two conditions are not associated

TREATMENT OF DIABETES Certain specific adjustments of the diet and insulin are often necessary during chronic disorders which accompany diabetes

Dietary Adjustments Obesity requires caloric restriction The detail of this adjustment has been discussed in a previous section It is of practical importance not only for correction of obesity itself but as a therapeutic aid in the treatment of most cardiac vascular and hypertensive complications Certain orthopedic infectious and vascular defects of the legs and feet require reduction of the weight

Pregnancy and lactation demand increases in the caloric intake sufficiently great to maintain weight at normal levels

Chronic infections usually require a greater caloric and protein intake than normal Both should be increased by 25 to 50 per cent over customary levels The behavior of the body weight is the most satisfactory measure of the adequacy of the diet Pulmonary tuberculosis is particularly important in this respect although the same dietary adjustments are indicated in any chronic infectious disease in which normal nutrition is difficult to maintain

Protein deficiency states demand specific increases in the diet protein to levels of 1 5 to 2 gm per kilogram of body weight per day in adults and correspondingly higher amounts in children This diet correction is applicable in conditions associated with albumin loss certain types of hepatic disease and anemia in pregnancy after starvation and in hyperthyroidism and chronic infections Renal insufficiency with nitrogen retention or uremic tendencies demands restriction of the protein to about 0 5 gm per kilogram per day unless hypoproteinemia also exists In the latter case the lesser of two evils must be selected

Carbohydrate increases are indicated occasionally particularly before and after thyroid and biliary tract surgery and after any infectious or malnutrition state which depletes liver glycogen Carbohydrate to fat ratios double those ordinarily selected should then be used until the deficiency is considered to be corrected

Gastro intestinal complications generally require appropriate restriction in the selection of food but no change in the fuel [illegible] of the diet from those ordinarily used in tr[illegible] of diabetes

Insulin Adjustments During infections,

amount used under ordinary conditions Doubling or tripling the dosage is not at all unusual Daily dosages in the hundreds or even thousands of units are rarely required "Insulin resistance" (refractoriness insensitivity) is then considered to exist Correction of abnormally high hyperglycemia and glycosuria by the use of adequate insulin sometimes makes the difference between satisfactory and unsatisfactory progress in the complicating illness particularly in those of an infectious nature Late in pregnancy the lowered "threshold for sugar excretion demands that blood sugar levels be used in measuring the response to increased insulin Renal glycosuria may be misleading

Certain chronic complications likewise demand that less insulin than usual be used in diabetes Obviously any condition which interferes with the customary intake of food will do so In most cerebrovascular and cardiovascular complications it is prudent to lower insulin dosages cautiously and permit moderate hyperglycemia to exist as a cushion

sitivity and so reduce the amount of insulin needed, sometimes radically The termination of pregnancy usually demands rapid reduction in previously increased insulin dosage

Treatment of Complications Some specific differences in therapy of chronic diseases occurring in diabetic patients deserve special emphasis

Vascular Disease The management of arterial hypertension in diabetes does not differ from that of hypertension in general Inasmuch as many older diabetic patients are obese reduction of weight is one of the few measures which accomplishes anything None of the other measures usually used in attempts to control hypertension conflict with the treatment of diabetes Surgery should be performed only under conditions of strict control of hyperglycemia and glycosuria

Excessive use of coffee, so common with diabetics on restricted diets, should be stopped None of the vasodilator or sedative drugs interfere with diabetic management, provided they are not dispensed in vehicles containing sugar

Cardiac Disease In the management of heart disease in diabetic patients obesity frequently requires correction and carbohydrate restriction should not be severe Bed

tion of normal activity after rest and compensation Digitalis quinidine ammonium chloride, mercurial diuretics vasodilators opiates, and barbiturates all are virtually without effect on sugar balance and act the same as in similar nondiabetic conditions

Polyneuritis In common with practically all neurologic diseases occurring in diabetic patients the treatment of diabetic polyneuritis is just about as ineffective as anything in the entire field of medicine Restoration of normal sugar balance does not help and actually may precipitate an attack Rest and heat are of some value In severe attacks the only measure which provides substantial relief from pain is the use of sedatives frequently, in large doses, and over considerable periods of time

Severe attacks of neuritis ordinarily are uninfluenced by vitamin therapy but large parenteral doses of thiamine chloride should be tried, as occasionally patients are relieved by it Mild attacks consisting of vague pains in the extremities may be relieved dramatically by vitamin B therapy

Ocular Complications Transient errors of refraction due to changing water balance in the lens frequently accompany rapid desugarization The disturbance of vision almost always corrects itself spontaneously in the course of a few weeks with no treatment except maintenance of approximately normal sugar balance Suitable lenses correct the refractive error temporarily But it is fruitless to fit lenses at the height of the visual error because it changes quantitatively from day to day owing to constantly changing conditions within the eyeball The best treatment, if the error is proved to be refractive, is to reassure the patient, do nothing for 2 to 4 weeks, then refract the eyes on two

type of refractive error, and the difference often is in the direction of normal

The treatment of permanent, mature lens cataracts is the same in the presence of diabetes mellitus as in nondiabetic patients In expert hands cataract removal is a perfectly safe procedure, provided the diabetes is controlled properly Because of the frequent association of cataracts and retinal pathology, the condition of the retina should be estimated carefully before removal of the lens Sometimes the retinal condition cannot be judged because of the cataract In that case, it seems legitimate to remove one lens, but defer judgment on possible restoration of vision until the retina can be seen

Glycosuria and excessive hyperglycemia must be corrected preoperatively and postoperatively, according to the principles for any surgical procedure The lens removal and the postoperative care must be conducted with a minimum of trauma to the eye because of the great danger of hemorrhage due to vascular disease or hypertension or both During the immediate postoperative period a small margin of hyperglycemic protection against insulin shock is less dangerous than hypoglycemia because of the risk of hemorrhage within the eye Infection occurs at times Enucleation is occasionally necessary because of persistent ophthalmitis from hemorrhage or infection The risks of lens removal for cataract are somewhat greater in diabetic than in nondiabetic patients chiefly for the reasons described

The treatment of retinitis in diabetes is most unsatisfactory The value of diets high in protein is suggested by the studies of Schneider Lewis, and McCullagh with serum proteins in human and experimental diabetes Vitamin C and rutin should be prescribed, although no uniform improvement has yet been demonstrated due to their use Occasional patients have improved with

objectives of treatment is reduction of elevated blood pressure by any means possible with safety

The prevention of retinitis and the means of improving it after it has appeared must wait for a better understanding of the reasons for its occurrence in diabetes Until then every effort should be made to correct known metabolic abnormalities by proved methods of dietary and insulin control Hypoglycemia should be avoided, of course

Glomerulosclerosis The treatment of intercapillary glomerulosclerosis is fundamentally the same as that of any form of chronic nephritis Heavy loss of albumin with hypoproteinemia and edema should be replaced by means of high protein feedings or blood plasma injections Sodium restriction, acid-ash diets and mercurial diuretics are effective in the relief of edema Digitalization and bed rest may be required if congestive heart failure on an arteriosclerotic or hypertensive basis accompanies the renal disease,

proteinemia is not present

Gangrene The treatment of unmistakable dry gangrene is to maintain sterile conditions if possible protect from injury, swelling, and chilling use the best of the various methods available for promoting the formation of collateral circulation, watch for suppuration and wait for clear cut demarcation to occur If the lesion escapes infection and demarcation is satisfactory, amputation at the line of demarcation may be attempted, using great care not to injure healthy tissues proximal to the lesion any more than is necessary Infection or gangrene of the stump is likely to result from this procedure and it should not be attempted until the tissue proximal to the lesion is in excellent condition

After amputation the stump should be left open and packed with a water soluble sulfonamide ointment such as sulfa-carbowax (3 per cent sulfathiazole and 3 per cent sulfadiazine in carbowax, a water soluble hydrocarbon ointment base made by the Union Carbon and Carbide Company) A

Infections The treatment of infected lesions varies somewhat with the detailed conditions present The procedure of greatest value is continuous warm moist compresses of generous thickness, kept warm with an automatic heat cradle, and not permitted to dry out For this purpose the most satisfactory technic in the author's experience has been the use of generous thicknesses of soft compress material wrung fairly dry after immersion in saturated aqueous magnesium sulfate solution A waterproof layer of thin material, such as rubber sheeting or waxed paper, is wrapped around the moist compress and the entire dressing then enclosed snugly in a warm, dry outer dressing to keep it moist and warm An automatic heat cradle or other device can then be placed over the foot and leg to prevent cooling The compresses should be changed every 2 or 3 hours If maceration of the skin occurs, compresses should be discontinued for a day or so The foot should be elevated and at complete rest

Next in importance to warm moist heat, elevation, and rest is judicious drainage of suppurating lesions Whether suppuration occurs superficially in or under the epidermal layer or whether it is in deeper layers of the toe, foot, or leg, it should be drained as promptly as possible, but with a minimum of trauma to uninvolved tissue When a suppurative cavity with a thin roof can be demonstrated, it should be incised conservatively, necrotic sloughs excised without trauma to adjacent walls, and satisfactory drainage established Packing the cavity with the chemotherapeutic agents described above, or continued warm, moist compresses should follow incision and debridement Ordinary surgical principles for suppurative infection should be applied with the additional precaution of extreme care to avoid any injury which is not essential to provide drainage Sloughs should be allowed to separate rather than cause injury of viable tissues to which they are attached Drainage should be conservative rather than radical, unless it can be accomplished through necrotic tissues Moist heat is preferable to dry heat after incision, and absolute rest and elevation of the extremity must be maintained until active granulation and epithelization begin

Chemotherapy has become indispensabl in the treatment of infected lesions of th extremities in diabetes, with or withou gangrene Penicillin, streptomycin, and th sulfonamides used generally or locally shoul be selected according to the organism pre ent The use of chemotherapeutic agent intra arterially in the affected extremity an by local infiltration into and around th lesion have been reported to be of benefi It is difficult to maintain effective concen trations by these methods, however, and th latter is theoretically subject to the crit cism of causing local trauma and spreadin infection

Amputation is indicated if any of the fol lowing sets of conditions are present

(1) Rapid extension of infection up th leg in spite of local therapeutic meas ures, threatening sepsis or metastati infection
(2) Intractable pain of long duration wit poor prognosis for the extremity
(3) Unsuccessful treatment of a localize lesion with the probability that heal ing will never occur, osteomyelitis i one of the most common reasons fo such lack of progress
(4) The probability of a poor functiona result even though healing of th lesion can be accomplished
(5) Recurrent lesions in the same ex tremity resulting in complete dis ability

When the extremity must be sacrificed fo any of these reasons, the choice of the leve of amputation depends on the character o the lesion and the blood supply in the indi vidual case If the lesion is limited to a digit, the blood supply is good, and no infection exists proximal to the base, the digit alone can be amputated, preferabl through the head of the metatarsal

If infection or gangrene of the foot (par ticularly on the dorsum) has become resist ant to local treatment or endangers life by extension proximally, amputation of the leg becomes necessary In rare instances with exceptionally good blood supply and no gangrene an amputation through the foot or ankle is justified, but ordinarily it leads to the necessity for reamputation if done so low in a foot with obliterative arterial disease

Amputation above the knee probably is the safest procedure when blood supply is poor although recently excellent results ' — ol t uned in skillful and expen — ⅄ lla of est ı of ınce of tension due to eucı a u ties and closure of the stump by means of a small drain

Refrigeration of an infected gangrenous extremity is advantageous for preservation of the leg if amputation must be delayed for any reason for reduction in toxemia and for relief of pain It is of no particular value in local treatment or as anesthesia and it may result in further impairment of blood supply at the amputation level Its chief indications and effects are the same as those for amputation and removal of the leg under spinal or safe general anesthesia ordinarily is preferable

The prognosis of trophic lesions of the feet is excellent as a rule even though the bones are involved With débridement and protection from trauma and infection superficial lesions heal in a week or two Deep lesions with adherent sloughs may take several weeks or even months to heal and aseptic necrosis of the bones of the foot invariably heals in time if not injured or infected Gentle dissection and separation of the necrotic skin forming the adherent sloughs in the deep skin lesions aid in the healing of these persistent lesions Dissection must be accomplished however without trauma to surrounding tissues or introduction of infection

Infectious Diseases The management of diabetes complicated by tuberculosis varies from that ordinarily prescribed only in so far as higher diets and more exact adjustment of sugar metabolism are desirable

Body weight and nitrogen balance are more difficult to maintain because of the increased metabolism so frequently accompanying the infection Instead of the usual 25 to 30 calories per kilogram per day 40 or 50 may be required for normal nutrition in adults and correspondingly more in children The increased caloric requirement generally runs in direct proportion to the degree of fever and toxemia The protein intake should be 1.5 to 2 gm per kilogram per day for adults

Treatment of all urinary tract infections in diabetes consists of (1) elimination of glycosuria continuously (2) avoiding trauma and contamination whenever possible (3) the use of measures appropriate for the treatment of urinary infection in anyone without diabetes The first objective involves the intelligent application of ordinary or emergency methods of diet and insulin control as indicated by the character of the infection The second demands extreme caution on the part of the urologist surgeon gynecologist or internist in the use of instrumentation of the urinary tract The use of appropriate urinary antiseptics with in ~ ~tant in this ce of dia betes The u u ı treatment simply means that any method of treatment appropriate for infections of the urinary tract in nondiabetic patients may be applied equally well in diabetes provided that good —nl hed before

may be

Sulfonamides are ... sugar metabolism in nontoxic dosage Acid therapy must be used with caution whenever ketogenic or uremic acidosis threatens or has existed recently but are perfectly safe if the alkali reserve is normal and ketogenic acidosis is prevented postoperatively If diabetes is kept under good control endoscopy and surgical manipulations are fully as safe and effective as in patients without diabetes

It is important to search for fungous infection between the toes and other skin folds and eliminate it before it leads to pyogenic infection The usual methods of treatment are effective except that strong fungicides which may be irritating in themselves should be avoided as all forms of chemical thermal and mechanical trauma in feet which have

vulvar itis and out local therapy marked dermatitis the lesions persist even after desugarization, and further local treatment

required For the acute stages warm compresses of 0 5 per cent borax in water (1 teaspoon to 1 qt of water) are effective Hot sitz baths in borax solution may also be used When acute inflammation subsides daily painting of the lesions with 1 or 2 per cent tincture of gentian violet usually clears the residue of monilial infection without further difficulty The best preventive treatment is avoidance of glycosuria

Lipoid and Allergic Disorders Xanthomas undergo involution and disappear leaving pigmented scars when blood fats are reduced to normal by good control of glucose metabolism with insulin Low fat diets probably aid in the restoration of blood fat levels to normal but undoubtedly adequate glucose utilization is more important These lesions now are seen much more rarely because of the prevention of extreme hyperlipemia owing to better control of sugar metabolism

Necrobiosis lipoidica diabeticorum is uninfluenced by any local treatment and control of the diabetes has no effect on it The lesions occasionally recede spontaneously leaving atrophic skin Ulceration may occur

Prevention of insulin atrophy is possible by systematic rotation of injection sites so that no area of the skin receives insulin more often than once every 2 or 3 weeks This is unnecessary in patients who are free from any tendency toward atrophy but in those who are susceptible it is the only known method of preventing marked disfigurement When atrophy has already occurred insulin may be injected into the abdominal wall where cosmetic defects are unimportant

Lipomas due to repeated injections of insulin into the same location should be prevented like atrophy by systematic rotation of the injection site and by frequent examination especially in children to be sure that this is being done Once they form they are relatively permanent

When generalized urticaria is linked unmistakably with any given insulin preparation substitution of another form or brand of insulin may eliminate the difficulty If all forms of insulin cause difficulty desensitization can be accomplished within a day or so by injections of gradually increasing doses every half hour or hour according to the dosage schedule shown in Table VII

TABLE VII *

DESENSITIZATION TO INSULIN

Dilution of Insulin †	*Subcutaneous Dosage at One half to One hour Intervals*
1 100 000	0 1 cc increasing to 1 cc by 0 1 cc additions
1 10 000	" "
1 1 000	" " " " "
1 100	" " " " " "
1 10 ‡	" " "
Undiluted ‡	"

* See footnote Table II
† In normal saline
‡ Increase interval between injections sufficiently to avoid hypoglycemia

Local allergic reactions due to insulin often fail to occur if the insulin is injected into the loose areolar tissue under the fatty panniculus instead of into the fat as the ordinary injection is made For this purpose a longer needle (¾ to 1 in) is necessary and the injection must be made into the side of the fold of the skin under the fingers which lift [illegible] fold between [illegible] of another [illegible] may stop the lesions In the order of their tendency to cause reactions of this type the various insulin preparations may be listed as follows protamine zinc insulin protamine insulin mixtures globin insulin regular insulin solution of zinc insulin crystals

If neither of these two devices stops the formation of the wheals and *desensitization* as described above is impracticable persistence *in the use of the offending insulin* preparation usually accomplishes desensiti

zation automatically in the course of a few weeks The tendency almost always disappears in the course of time even with the most sensitive individuals

Pregnancy Control of the diabetes and nutritional status of the pregnant diabetic woman involves (1) increases in the diet as indicated by the body weight (allowing for edema and polyhydramnion) especially during the latter half of pregnancy (2) elimination of abnormal hyperglycemia and glycosuria in so far as possible without insulin shock and unendurable inconveniences (3) respect for the renal type of glycosuria which commonly occurs near term

The experience of White indicates that hormonal replacement therapy should be prescribed in addition Stilbestrol and progesterone are both given in daily doses of 5 mg of each up to the 20th week of pregnancy Thereafter the dosage of each is increased by 5 mg every fourth week until parturition when a total dosage of 30 to 50 mg is given daily During infections with fever the dosage should be doubled In a large group of patients so treated the fetal survival rate has increased from about 50 to 90 per cent and the toxemia rate has fallen from about 50 to 5 per cent More recently the use of stilbestrol alone in dos

The two most important obstetrical problems demand decisions regarding the optimal time and the best method of delivery The size of the fetus and its tendency to premature death in utero loom large in influencing both of these decisions

The size of the baby should not be judged by the size of the abdomen or the weight of the patient because of the prevalence of polyhydramnion under these conditions *Radiologic as well as palpatory evidence* should be relied on If the infant is judged to be large as is often the case premature delivery is indicated White advises delivery in the 37th week of gestation unless the baby is determined to be unusually large in which case it is accomplished even earlier Because of the high incidence of fetal death in utero this policy seems wise

The route of delivery should be determined by the size of the fetus previous obstetrical experiences in the same patient the pelvic measurements the position of the fetus and the degree of effacement of the cervix at the time delivery is considered to be opportune In a high percentage of patients the net result of weighing this evidence determines that abdominal delivery by cesarean section is the method of choice Two thirds of the patients in White s series have been delivered by section under spinal anesthesia and without preliminary medication If normal labor occurs small amounts of barbiturate and scopolamine are used and the third stage is conducted under spinal or gas oxygen anesthesia The diabetes must be managed by the same emergency methods required for any other type of surgery with generous amounts of carbohydrate particularly if a long difficult labor ensues

The treatment of neonatal complications is suggested by their character Sedation during surgical delivery must be used sparingly and oxygen freely Prompt postural and mechanical clearing of the upper air passages seems to be far more important than is usually the case after delivery Restriction of fluids after delivery is indicated and weight loss welcomed if the infant is edematous Glucose subcutaneously or orally should always be given and the response observed if abnormal lethargy cyanosis or convulsive states appear The response to glucose is more reliable as an indication of hypoglycemia than the blood sugar level because the latter normally varies from 40 to 70 mg per 100 cc of blood soon after birth If dramatic improvement occurs with glucose it must be repeated at frequent intervals either by mouth by gavage or parenterally until symptoms stop recurring *between feedings Finally atelectasis must* always be suspected if cyanosis is present even though the air passages are clear In addition to oxygen a mixture of 5 per cent carbon dioxide in oxygen for a few minutes out of each hour may be of lifesaving importance

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HEMOCHROMATOSIS

There is no specific treatment for hemochromatosis Mallory s theory that it is due to chronic copper intoxication suggests that a search should be made for this metal in the patient s intake

The diabetes so frequently associated should be managed by orthodox methods Marked improvement can be expected temporarily with good nutrition and control of abnormal hyperglycemia and glycosuria Insulin resistance is seen not infrequently possibly as a result of liver damage Massive maintenance doses of insulin then may be required They should be employed without hesitation if the glycosuria fails to respond to ordinary dosage

Diets containing at least 200 gm carbohydrate and 100 gm protein daily help to prevent and correct hepatic damage Choline or methionine should be given in dosage of 3 to 6 gm daily Gratifying results in male patients with hemochromatosis have been reported after therapy with testosterone 25 mg three to five times weekly should be administered by intramuscular injection for a trial period of several weeks and continued at a somewhat lower rate if encouraging signs are evident Ascites may demand paracentesis

Usually however, unless improvement can be obtained by correction of the diabetic state the results of treatment are discouraging in proved hemochromatosis

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HYPERINSULINISM

Hyperinsulinism may be characterized as a definite clinical entity while a spontaneous (functional) hypoglycemia may result from [illegible]

Whatever the origin of a hypoglycemia the symptoms for a given blood sugar level of some duration are essentially the same They are a result of the effect of an inadequate plasma and interstitial fluid glucose level on nervous tissue In mild attacks sweating flushing palpitation etc perhaps all the result of a hypoglycemic epinephrine discharge predominate In severe attacks thick speech muscle spasm etc are prominent and eventually result in coma and death

Hyperinsulinism in the true sense may occur as a compensatory secretory reaction or a result of a temporary hyperplasia of the islands of Langerhans in infants born to mothers with uncontrolled diabetes (i e with chronic hyperglycemia) This functional hyperinsulinism is becoming increasingly rare with the more adequate control of diabetics during pregnancy The chief problem is the rapid recognition of the ailment at birth or of its possibility prior to delivery If normal feeding plus glucose therapy is adequate during the first 4 days of life the danger of a fatal outcome from this temporary type of hyperinsulinism is largely removed

The clinical complex generally thought of as hyperinsulinism and which is due to hyperfunction hyperplasia or tumors of the islands of Langerhans is of a chronic nature It is a rare disease with a silent onset In the first attack the hypoglycemia may lead to loss of consciousness but milder episodes usually initiate the ailment Diagnosis may not be easy and is essential for proper therapy The fasting blood sugar should be below 60 mg per 100 cc Symptoms of a hypoglycemia accompanied by a blood sugar level below 40 mg per 100 cc are evidence for hyperinsulinism "Hypoglycemic attacks brought on by long periods without food (omission of breakfast) and by moderate exercise point in the same direction Immediate relief from hypoglycemic symptoms by the intravenous injection of glucose solution is an important test A routine glucose tolerance test may complete the diagnosis but Conn has stressed the importance of a glucose tolerance test carried out under standard conditions Duncan gives 350 gm carbohydrate 1 25 gm protein per kilogram of body weight and f to a total of 35 calories per kilogram of body weight per day for 3 days prior to the glucose tolerance test Under these conditions a patient with hyperinsulinism has a subnormal fasting blood sugar level a test peak not over 120 mg per 100 cc and a return to subnormal values within 3 hours which is then maintained for several hours Some of the conditions in which different results are obtained are outlined under functional hypoglycemia As another diagnostic point Duncan adds the remarkable rate at which intravenously administered glucose is disposed of in hyperinsulinism

hydrate in much the same way as an overdose of insulin If the patient is in coma, intravenous administration of a glucose solution is necessary Epinephrine is no more useful than for an overdose of insulin in the diabetic Although a special diet is effective in many cases of functional hypoglycemia, it is futile in hyperinsulinism due to islet cell tumors Preparation for the operation entails the giving of large amounts of protein and slowly absorbed carbohydrate (bread cereal fruits) every 3 or 4 hours for at least

noma of the islands of Langerhans Since these tumors easily become malignant an operation should never be delayed when it is indicated When neither an adenoma nor a carcinomatous nodule is located at the time of surgery partial resection of the pancreas has been advocated by Wilder This may lead to the development of diabetes which may be controlled with diet and insulin The intravenous administration of 10 per cent glucose solution is useful during surgery and insulin may be needed in small amounts for a few days postoperatively It is generally unnecessary No drugs of any kind are efficacious in treating hyperinsulinism

Functional Hypoglycemia Functional hypoglycemia differs from hyperinsulinism in that there is no absolute overproduction of insulin concerned in the pathogenesis of the lowered blood sugar level and with the exception of one group of cases a high carbohydrate intake is desirable therapy There are many causes of functional hypoglycemia

and the treatment, if any, varies with the origin

Relative hyperinsulinism is a common cause of functional hypoglycemia Insulin secretion is not abnormal but is sufficiently high for the existing conditions to be in excess of opposing factors and thus cause hypoglycemia

When intravenous glucose therapy which has been continued for some time is suddenly stopped, particularly in infants or children, a transient physiologic hyperinsulinism may exist for a time and hypoglycemia result The same effect may be observed in undernourished subjects or after short periods of fasting as postoperatively when glucose solutions are used for restoration of the fluid balance The hypoglycemia following the sudden discontinuance of glucose therapy has little clinical interest and is easily prevented or controlled by a slower withdrawal of the glucose therapy

A number of endocrine diseases may lead to severe hyperglycemia based on relative hyperinsulinism A rare but typical example of this state is Simmond s disease or hypophyseal cachexia which occurs with atrophy of the anterior pituitary gland Tumors of the anterior lobe may have a similar effect In either case the hypoglycemia is a secondary feature of the disease and fails to confuse the clinical diagnosis or govern the therapy

Addison's disease or adrenal insufficiency may cause a hypoglycemia much as does anterior pituitary deficiency, by removing a normal insulin opposing secretion The other clinical features make it possible to classify such patients properly

Hypothyroidism especially following thyroidectomy for Graves's disease may occasionally give rise to the clinical symptoms of hypoglycemia Other symptoms should make it possible to reach the proper diagnosis and thyroid therapy rapidly corrects the hypoglycemia

A lack of carbohydrate food due to starvation or food loss by vomiting or diarrhea is frequently the cause of mild clinical evidences of hypoglycemia Except for the immediate use of glucose to combat the acute symptoms a consideration of the treatment [illegible]

during lactation In both cases the possibility of hypoglycemia should be kept in mind and if symptoms occur, an increase in the number of meals per day, with or without an increased total food intake, is indicated

Liver disease must be severe to be the cause but is not infrequently the origin of a mild hypoglycemia The liver normally is a most important factor in the blood sugar regulation, removing sugar to form glycogen during hyperglycemia and forming sugar from carbohydrate or protein sources when a low blood sugar concentration indicates that it is needed If sufficient liver tissue is destroyed or physiologically inactivated, the hepatic blood sugar regulating mechanism may be upset sufficiently to give rise to a chronic hypoglycemia Acute yellow atrophy, grossly disseminated hepatic or metastatic tumors or other extensive diseases of the liver cause an obvious hypoglycemia Ascending cholangitis infections, hepatitis, and cirrhosis of the liver are the more common offenders Diagnosis may at times be difficult As in hyperinsulinism acute symptoms are controlled by glucose injections, fasting blood sugar levels are subnormal, and glucose tolerance tests return to hypoglycemic levels The real distinction is that unlike hyperinsulinism, patients with liver disease and hypoglycemia have glucose tolerance tests which are diabetic in nature, rising to high levels for several hours after the ingestion of the glucose, showing an impaired ability to remove glucose from the blood stream

The treatment of the hypoglycemia of liver disease is unlike that for hyperinsulinism in that a low fat intake is essential The fat intake can have no direct influence upon the hypoglycemia and if at a normal level or higher, can be deleterious to the course of the liver ailment A liberal protein intake [illegible]

supplied indefinitely by carbohydrate, but to protect the liver from further damage The daily carbohydrate intake may be as high as is necessary to prevent symptoms of hypoglycemia If the ailment necessitates an operative procedure such as cholecystectomy, preoperative treatment also includes a high carbohydrate intake (to 500 gm per day)

and as much protein as the patient can take

Diseases of the nervous system occasionally give rise to hypoglycemia Intracranial injuries, subdural hemorrhage, and general paresis are the most common examples The *low blood sugar level rarely confuses the* diagnosis and treatment of this disturbance as such is never necessary

Functional disturbances of the sympathetic nervous system provide the largest group of patients presumed to have chronic hypoglycemia They comprise those individuals with neurocirculatory asthenia vagotonia, and various neuroses The bulk of them suffer *from mild "hypoglycemic" symptoms* but have no hypoglycemia Carbohydrate or other food fails to relieve their symptoms (weakness, fatigue, palpitation, etc), and *they feel faint without reference to meals* Neither fasting nor physical exercise provokes their symptoms and fasting blood sugar *values are not abnormal*

Some patients in the neuroses group do suffer from mild degrees of hypoglycemia and have flat glucose tolerance curves Conn has designated the hypoglycemia of neurosis as a functional hyperinsulinism but it would seem more reasonable to assume that it is associated with the vagotonia or other disturbances of the sympathetic nervous system In any case a special diet gives relief to practically all of these patients Conn suggests that for the average adult the carbohydrate content should not exceed 150 gm per day and is best provided in a nonsugar and slowly absorbable form (e g, bread, cereals, fruit, etc) High protein (120 to 140 gm per day) and fat contents (170 to 200 gm) are recommended The carbohydrate content is kept low because glucose stimulates sugar storage and contributes to the hypoglycemia The high protein content is based on the slow metabolism and steady release of glucose formers by this element of the diet Waters first reported on the use of a high fat diet which Wilder had already used at the suggestion of his dietitian The rationale of the high fat content may be a reduction in the emptying time of the stomach with a consequent slower release to the circulation of the carbohydrate in the diet

Of even more importance than the composition of the diet used in combating neurotic hypoglycemia is the quantity of food The total diet should have a high caloric value, at least 30 to 40 calories per kilogram of body weight Any increase in body weight if the patient is underweight and a moderate increase if already of normal weight may contribute to a marked amelioration of symptoms The diet can be divided into three meals and three nourishments in midmorning midafternoon, and on retiring

Physical exercise which lowers the blood *sugar should be restricted until the hypoglycemia* has been controlled If exercise cannot be avoided, extra carbohydrate food should be taken a short time beforehand *There are no drugs* which are directly useful in the treatment of patients with hypoglycemia Epinephrine is no exception for its effect is of short duration and dependent on the carbohydrate stores in the patient's liver

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OBESITY

Whatever the underlying cause, obesity in the last analysis is solely a question of a disturbance in the normal relation of the appetite to the energy expenditure The obese patient eats too much The adipose tissue is the normal depository for fat and in the obese this fat deposition is excessive The extra fat in the adipose tissue may be unusual in its distribution but in most cases it follows normal variations

Etiology as a Basis of Therapy Why do

fat people eat too much? This remains a *question about which we must speculate* An attractive hypothesis concerns a possible difference in the lipophilic activity (avidity for fat deposition and retention) of the adipose tissue of obese individuals At the present there is no evidence for this theory although the lipophilic quality of adipose tissue from different parts of the body differs markedly and this characteristic is retained on transplantation of these regional tissues It is easy to visualize similar variations of a hereditary or constitutional nature which could lead to obesity Granting that heredity is an important factor in body build Newburgh denies that it determines the presence of obesity

The evidence for endocrine factors as causes of obesity is not at all convincing at the present time There are suggestions that the pituitary adrenals pancreas and gonads may influence the deposition of fat but Cushing s disease is almost the only example of true endocrine obesity There is no evidence which would warrant the use of endocrine preparations in the treatment of obesity

Better food absorption or more efficiency in energy metabolism have both been used as explanations of the fat patient s plight No convincing evidence in support of these conceptions has ever been brought forward

For the present at least we are limited to the conception of an abnormal appetite as the cause of obesity Like many important self regulatory functions the appetite appears to be centered in the hypothalamus The cerebral cortex exerts a modifying influence on the functions of the lower nervous centers and appetite is no exception This brings up the question of psychologic factors in the origin of obesity This subject has been well studied in children and such factors are obvious to anyone who treats the obese at any age In spite of this fact psychiatric treatment has aided us little in weight reduction Diet accompanied by accessory measures is the basis of therapy

Objectionable Therapy Endocrine products with the exception of thyroid preparations when they are used for their calorigenic effect are not indicated as aids to weight loss in obesity

Ipecac emetine belladonna preparations digitalis dinitrophenol saline cathartics etc have all had their advocates but are contraindicated in the weight reduction program

Heat cabinet baths to reduce body weight are ill advised Water restriction as well as administration of diuretics to promote water loss are also undesirable

Exercise has often been recommended as a means of increasing the energy expenditure Unfortunately it usually increases the

and subcutaneous tissues

Accessory Therapy The energy expenditure may be increased by thyroid administration the drug acting as a pharmacologic calorigenic agent and not as an endocrine replacement It causes body protein loss and has many undesirable side effects Most workers oppose its use and there are definite objections to its administration to obese children It is well to remember that thyroid medication can replace the secretion of thyroglobulin by the normal thyroid gland and when the drug is discontinued the basal metabolic rate may fall far below normal Obesity does not stem from hypothyroidism and patients with this disturbance are rarely obese If one feels that thyroid medication must be used doses of 1 to 3 grains of desiccated thyroid U S P per day are suitable

significant degree of cardiovascular disease is allowed such medication

An extensive literature has accumulated on the use of sympathomimetic amines in the treatment of obesity Desoxyephedrine and *propadrine hydrochloride have had* their proponents but are now in the discard Amphetamine (benzedrine sulfate) has given good results for 13 years and more recently the dextrorotatory optical isomer (dexedrine sulfate) which appears to have fewer undesirable side effects has come into wide use The dosage is 5 to 30 mg daily (usually 10 to 20 mg of dexedrine sulfate) divided into at least two and sometimes three doses The drugs are never given after late afternoon for they may cause sleeplessness

Some patients are unable to take the amphetamine preparations because of undesirable excitatory effects These drugs may cause transient and minor increases in the blood pressure and basal metabolic rate but these effects are rarely troublesome and apparently unrelated to their effect in obesity Various explanations of the mechanism of amphetamine action in obesity control have been advanced but it is now accepted to be of cerebral origin It has some effect upon the appetite of the normal subject but is much more efficacious in the person who obtains excessive satisfaction from eating

There are some patients in whom amphetamine appears to reduce the appetite without *any attention to the diet* These people are few in number and the drug is most useful as an adjunct to the low calorie diet

fectiveness after prolonged use but following a rest period of several weeks its efficacy may be restored In any case, the use of amphetamine is a secondary weapon in weight reduction The low calorie diet is far more important than any form of drug therapy in the management of obesity

Diet Therapy Weight can always be reduced if the patient will adhere to a restricted diet The patient should desire to lose weight and his physician must believe in the therapy used It may be necessary to stress the health hazards and social objections to overweight Unless a person has become obese because of a true neurosis, the usual explanations and discussions with a patient will suffice to cause him to undertake a strict reduction regimen

Regular visits to the physician are essential They serve to maintain the patient's morale, as a check on this adherence to the *regimen* and afford an opportunity to answer questions which may arise An example is the depressing circumstance in occasional cases of water retention so that for some days or weeks the loss of body fat is not evident in daily or weekly weighing It is wise to explain this possibility in advance

Excluding the obese patient who resembles the uncontrollable chronic alcoholic, the difficulty of most obese *patients in fol*lowing a dietary regime is in breaking long established eating habits This is particularly true during the first 4 to 6 weeks of dieting and the control of the hunger sensation is most important during this period In a popular proprietary preparation small quan

the appetite Another proprietary remedy includes vitamins and minerals but it is not effective in reducing the appetite Bulk

questionable answer to hunger control However reducing diets tend to result in mild constipation and the all around effect of *these bulking agents is generally good* Two or 3 glasses of water satisfy hunger pangs for a short time and most patients may use *black coffee or plain tea if they prefer*

The food ingredient with the highest

some promise

A reasonably well balanced diet is desirable for weight reduction With the extremely low calorie levels (less than 1000 calories) it should be accurately weighed For less drastic regimes a diet made up of approximate portions will suffice The greatest success in treating obesity has been achieved when the calories are sharply limited even to 450 calories per day This is difficult for most patients and 600 calories or even *900 calories is to be preferred* for the minimum Protein is provided in the amount of not less than 1 gm per kilogram per day *for with this* quantity nitrogen balance is maintained Not more than 20 per cent of the calories are fat, in order to have carbohydrate for bulk and to prevent ketosis The carbohydrate is best supplied by low carbohydrate fruits and vegetables because of their bulk With the lower calorie diets non therapeutic doses of the fat *soluble and* B vitamins are useful food supplements Two good multiple vitamin capsules per day may be used If milk and its products are excluded to obtain a very low calorie or salt

intake, 1 to 2 gm of calcium phosphate each day is recommended

The stringency of the diet used will depend upon the age and general condition of the patient Children should not have their calories severely restricted Most reducing diets are ketogenic and the fewer the calories the greater their ketogenic action Although ketosis embarrasses obese subjects less than others, the development of a severe ketosis is undesirable in the child and in the female of any age, both of whom are rather susceptible to this condition

The disadvantages of obesity have been well analyzed but there are a few patients whose weight must be reduced slowly and with extreme caution These include aged subjects and patients with cirrhosis of the liver peptic ulcer and rarely chronic ulcerative colitis malignancy and active tuberculosis

Some obese patients will find it impossible to submit to a strict dietary regimen and others will choose to avoid the inconvenience and removal of their eating pleasure Except for a few whom the psychiatrist may aid if they can afford the time and expense we have nothing to offer these people They will have to keep their disease

When an obese patient has had his weight reduced to a normal level the job is not completed Without supervision the majority of once obese patients will quickly regain their weight A good basic diet should be prescribed for them and they should check with their physician at not longer than 6 month intervals In this way it is possible to maintain the results of a hard won battle with *occasional periods of mild dieting perhaps* 1400 to 1600 calories per day

800 Calorie Diet Form

(Carbohydrate = 67 Protein = 65 Fat = 31)

Breakfast	*Amount*
10 per cent fruit	1 serving (½ grapefruit 1 orange or ½ cup)
Egg	1
Toast	1 thin slice
10 00 A M	
Skim milk or butter milk	½ glass
Dinner	
5 or 10 per cent vegetable	2 servings (½ cup each)
10 per cent fruit	1 serving (as above)
Lean meat or cheese	1 medium serving
3 00 P M	
Skim milk or butter milk	1 glass
Supper	
5 per cent vegetable	2 servings (½ cup each)
10 per cent fruit	1 serving (as above)
Lean meat fish or cheese	1 large serving
8 00 P M	
Skim milk or butter milk	½ glass

Directions

No butter to be added to vegetables
Meats may be roasted broiled or stewed
Use only fresh fruits allowed or fruit canned without sugar
Vegetables to be prepared without cream cream sauce butter or salad dressing

1000 Calorie Reduction Diet

(Carbohydrates = 70 Fat = 51 Protein = 65)

Breakfast	*Amount*
Fruit 10 per cent	1 serving
Egg	1
Toast white or whole wheat	1 thin slice
Butter	½ teaspoon
Coffee	If desired
Dinner	
5 per cent or 10 per cent vegetables (One may be served as a salad)	2 servings (½ cup each)
10 per cent or 15 per cent fruit	1 serving
Eggs or Meat or cottage cheese	2 / 1 small serving
Butter	½ teaspoon
Milk	1 glass
Supper	
Broth	If desired
5 per cent or 10 per cent vegetables (One may be served as a salad)	2 servings (½ cup each)
10 per cent or 15 per cent fruit	1 serving
Lean meat fish poultry or cottage cheese	1 large serving
Butter	½ teaspoon
Milk	1 glass

Water clear broth vinegar tea, and coffee may be used as desired.

1000 Calorie Diet (*Cont'd*)

Meats may be roasted, broiled, or stewed
Use only fresh fruits allowed or fruit canned without sugar
Vegetables to be prepared without cream, cream sauce, or salad dressings
May use butter as allowed in diet

1200 Calorie Reduction Diet

(Carbohydrate = 95, Fat = 60, Protein = 70)

Breakfast	*Amounts*
Fruit, 10 per cent	1 serving
Egg	1
Toast, white or whole wheat	1 thin slice
Butter	½ teaspoon
Coffee	If desired
Dinner	
5 per cent or 10 per cent vegetables (One may be served as a salad)	2 servings (½ cup each)
10 per cent or 15 per cent fruit	1 serving
Eggs	2
or	
Meat or cottage cheese	1 small serving
Butter	½ teaspoon
Bread	1 thin slice
Milk	1 glass
Supper	
Broth	If desired
5 per cent or 10 per cent vegetables (One may be served as a salad)	*2 servings* (½ cup each)
10 per cent or 15 per cent fruit	1 serving
Lean meat, fish, poultry, *or cottage cheese*	*1 large serving*
Butter	½ teaspoon
Bread	1 thin slice
Milk	1 glass

Water, clear broth, vinegar, tea, and coffee may be used as desired
Meats may be roasted, broiled, or stewed
Use only fresh fruits allowed or fruit canned without sugar
Vegetables to be prepared without cream, cream sauce, or salad dressing
May use butter as allowed in diet

1500 Calorie Reduction Diet

(Carbohydrate = 118, Fat = 84, Protein = 80)

Breakfast	*Amounts*
Fruit, 10 per cent	1 serving
Egg	1
Toast, white or whole wheat	*1 thin slice*
Butter	1 teaspoon
or	
Bacon	3 strips
Cream	2 tablespoons
Coffee	If desired
Dinner	
5 per cent or 10 per cent vegetables (One may be served as a salad)	2 servings (½ cup each)
10 per cent or 15 per cent fruit	1 serving
Meat	1 *medium serving*
Butter	1 teaspoon
Bread	1 thin slice
Salad Dressing	1 teaspoon
Milk	1 glass
Supper	
Broth	*If desired*
5 per cent or 10 per cent vegetables (One may be served as a salad)	2 servings (½ cup each)
10 per cent or 15 per cent fruit	1 serving
Potato	1 medium
Lean meat, fish, poultry, or cottage cheese	1 large serving
Butter	1 teaspoon
Bread	1 thin slice
Milk	1 glass

Water, clear broth, vinegar, tea, and coffee may be used as desired
Meats may be roasted, broiled, or stewed
Use only fresh fruits allowed or fruit canned without sugar
Vegetables to be prepared without cream or cream sauce
May use butter as allowed in diet

Vegetables

5 Per cent	*10 Per cent*	*20 Per cent*
Asparagus	Beets	Corn
Artichokes	Carrots	Lima Beans
Beet greens	Kohl-rabi	*Baked Beans*
Broccoli	Parsley	Parsnips
Brussels sprouts	Peppers	Peas
Cabbage	Pumpkin	Potatoes
Cauliflower	Turnips	Squash Hubbard, Baked
Celery		
Celery cabbage		
Chard		
Cucumbers		
Cucumber pickles		
Dandelion greens		
Endive		
Eggplant		
Lettuce		
Mushrooms		
Okra		
Onions		
Radishes		
Rhubarb		
Sauerkraut		
Spinach		
String beans		
Tomatoes		
Watercress		
Wax beans		
Summer squash		

Fruits

Per cent	15 Per cent	20 Per cent
ntaloupe	Apples	Bananas
anberries	Apricots	Figs, fresh
oseberries	Blackberries	Grapes
apefruit	Blueberries	Grape juice
neydew	Cherries	Pomegranate
mons	Loganberries	Plums
mes	Peaches	Prunes, cooked
ranges	Pears	
rawberries	Pineapple	
atermelon	Raspberries	
nned Fruit *thout sugar*	Canned Fruit *without sugar*	
11 Per cent	*12 15 Per cent*	

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DIABETES INSIPIDUS

Diabetes insipidus results from an abnormal reduction in the secretion of the antidiuretic factor by the posterior lobe (pars nervosa) of the pituitary gland In the normal subject this hormone, secreted under the influence of the hypothalamus, insures adequate reabsorption of water by the renal tubules When the hormone is lacking polyuria ensues and secondary to this uncon- ... excessive thirst results ... s may ... urs as a familial disorder More often it is secondary to trauma or various disease processes such as meningitis, syphilis, or tumors The cause of the ailment is always destruction or damage to the pars nervosa of the pit... the supraoptichypophyseal tract

or the associated nuclei in the hypotha... The apparent necessity of a functioni... terior pituitary gland and the suppo... that it supplies a diuretic factor have ... been supported by a case of diabet... sipidus due to anterior pituitary overac...

If a patient is suffering from diabe... sipidus because of an obvious tumor, tr... developmental abnormality, infection ... thomatosis, or other process in the ... cephalopituitary area, the treatment ... disease *must involve the cause as w*... the symptoms If no underlying lesion ... covered, the treatment of which may ... in improvement or cure, we are limited ... attempt to control the polyuria and ...

... makes this easier or more effective r... restriction is of some value but must ... *companied by sodium chloride restr*... which of itself is far more important ... best results are obtained not alone b... exclusion of added salt from the diet (b... soda and baking powder also), but ... judicious selection of low salt foods s... the urine contains only a fraction of a ... *of sodium chloride* per day But som... restriction is better than none, and r... ... intake to ... ie c ... all ... he ... rest... because of their caffeine content I... case diet therapy is only palliative ... merely serves as an adjunct to therapy ... posterior pituitary preparations

Symptomatic Treatment· Substi... therapy with active antidiuretic prepar... of the posterior pituitary gives good c... of the symptoms in almost all patient... diabetes insipidus They usually have ... effects and in most cases may be con... indefinitely. Various preparations and ... forms are available

- Posterior pituitary injection (soluti... posterior pituitary) USP X... USP units per cubic centimeter
- "Pituitrin," for surgical use (Parke, ... & Co) 20 USP ...

meter twice the strength of U S P extract

Beta hypophamine N N R — Pitressin" (Parke Davis & Co) 10 pressor units per cubic centimeter

Beta hypophamine tannate — "Pitressin" tannate in oil (Parke Davis & Co) 5 pressor units per cubic centimeter

Posterior pituitary powder U S P

The original symptomatic treatment of patients suffering with diabetes insipidus made use of subcutaneous or intramuscular injections of aqueous posterior pituitary extract It is still used generally as "pitressin in doses of 0 5 to 4 cc daily A single dose affords relief from symptoms for 4 to 24 hours In most patients a morning and evening injection is required "Pitressin" has less of the undesirable stimulating action on the intestine found with the U S P or "surgical" extract

"Pitressin" tannate in oil is the injectable preparation of choice The injection of 1 cc (containing 5 pressor units) intramuscularly (never intravenously) will control the symptoms of the disease for 24 hours to 3 days Injections are rarely required more frequently than once a day The oil injections may be repeated as often as the symptoms require

Symptoms may be controlled by the intranasal use as a spray or on a swab of the aqueous posterior pituitary extracts A nasal tampon soaked with 1 cc of extract is placed against the roof of the nasopharynx two or three times daily The intranasal application method is not regularly effective and it is expensive

Nasal insufflation of posterior pituitary gland powder is an exceedingly good method of controlling the polyuria and thirst A dose of about 50 mg may be snuffed from the finger tip or administered with a powder atomizer or blower The Armour powder inhalator (Armour Laboratories) is specially designed for capsuled powders and posterior pituitary powder is available in this form The capsule is opened and placed in the chamber or in other blowers a 50 mg pinch of the bulk powder is placed in the instrument and the nozzle is introduced well into the nostril and so directed that its tip is pointed upward between the eyes A few puffs deposit the powder on the mucous membrane the anterior portion of the nasopharyngeal roof being covered The remainder of the powder is then blown into the opposite nostril Too vigorous blowing is avoided as it scatters the powder to nonabsorbing areas The patient experiences a slight stinging sensation "between the eyes" when the powder is correctly placed and he soon becomes expert in its application The powder is used at 4 hour intervals during the day and once during the night Continued use produces no local irritation and allergic manifestations have not been noted. The technic is simple convenient and without objectionable features A not inconsiderable feature of powder therapy is the low cost Intranasal medication is ineffective during a coryza and at such times hypodermic administration of a posterior pituitary preparation is necessary

Overdosage with posterior pituitary medications will not stop the urinary flow but patients should be cautioned to reduce their fluid intake to normal levels during treatment The large volume fluid intake necessary with uncontrolled diabetes insipidus may become a habit and if continued during therapy can lead to serious water intoxication Only enough water to satisfy the thirst should be taken

Some subjects appear to be sensitive to pituitary preparations and besides severe intestinal cramps and other gastro-intestinal reactions show cardiovascular symptoms For this reason it is wise to try a patient with a small dose of an aqueous extract before using "pitressin" tannate in oil When a patient continues to react unfavorably it may be necessary to give more frequent injections of smaller doses of extract. As a rule intranasal insufflation therapy will avoid untoward reactions This method also is free of the occasional atrophy of subcutaneous tissue around the site of numerous hypodermic injections in the same area Whether or not the anaphylactoid reactions reported from pituitary extract injections may be avoided by powder therapy has not been noted

Substitution therapy in diabetes insipidus by means of the antidiuretic *hormone* in the form of various posterior pituitary preparations is a palliative measure *It should* be considered in the same category as the use of insulin in diabetes mellitus The therapy

in both cases must be continued for the remainder of the patient's life except for the rare cases in which remissions may occur An exception is in diabetes insipidus secondary to a cause which may be successfully removed or treated

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ACIDOSIS AND ALKALOSIS

Physiologic Considerations as Related to Therapy Acidosis and alkalosis refer to disturbances of the acid base balance in the organism For practical purposes these terms correspond to acidemia and alkalemia A condition of extravascular acidosis or alkalosis may exist in various tissues for a limited time but by and large the reaction of the blood is representative of the alkalinity or acidity of the body as a whole

The body fluids are all alkaline but so nearly neutral that the total of the basic cations is practically equal to the sum of acid anions In the plasma and other extracellular fluids sodium is the chief base normally comprising 92 per cent of the cations The balance is made up of potassium cal

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second (22 per cent) while sulfates phosphates and proteins constitute the remainder It is obvious then that in acid base disturbances we are primarily concerned with the amount of sodium chloride and bicarbonate in the plasma

The acid base reaction or pH of the plasma is protected by the buffer salts of weak acids chiefly proteins bicarbonate and phosphate which can react with strong acids (e g HCl lactic ketone bodies) to give a neutral salt and a weak acid Increased respiratory output of CO_2 reduces the carbonic acid con

against extra base the respiratory output of

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in metabolism The kidneys are responsible for remedying the major disturbances in the acid base balance They do this first by excreting different ratios of secondary and primary sodium phosphate, depending on

whether base or acid should be lost by the organism and giving wide variations in the reaction of the urine Excess in organic base, usually sodium may be excreted as bicarbonate *without the loss of* plasma anion to the body Lastly the kidney may rid the body of excess acid by excreting ammonia with it in place of inorganic base

The mechanisms which protect the reaction of the blood always require some time for their effect and if the disturbance is *severe enough the compensating devices* are *unable to cope with it Conditions of acidosis* and alkalosis then result The various mechanisms producing acidosis and alkalosis will be outlined for these disturbances are best treated by removing the cause

Acidosis Acidosis is caused first by a primary CO_2 excess due to increased CO_2 production in the tissues and/or diminished *CO_2 output from the lungs This type of* acidosis occurs in morphine poisoning and similar depressions of the respiratory center when inadequate pulmonary ventilation leads to CO_2 retention This is also seen in a mild way during normal sleep and causes the usual acidity of night urine

In congestive heart failure pulmonary *edema sometimes fails to allow* the normal CO_2 loss through the alveoli

Some cases of emphysema and bronchitis have an abnormally *high alveolar CO_2* tension This in turn increases the blood CO_2 and being a chronic condition is compensated for by an increased bicarbonate content of the blood

An acid excess due to an increase of acids stronger than carbonic with a compensatory *secondary CO_2 deficit is the second cause of acidosis Typical examples of this type of* acidosis are the accumulation of organic acids such as formic in methyl alcohol poisoning, lactic acid in severe exercise, the ketosis of starvation, and acidosis in uncontrolled diabetes also due to the ketone bodies

Acidification with ammonium chloride in diuretic therapy purposely produces this type of acidosis The retention of nonvolatile acids such as phosphoric in renal insufficiency has a *similar* effect so far as the production of acidosis is concerned

Acute diarrhea, particularly in infants, often produces an acid *retention acidosis* It depends on the relative loss of water and *salt When water loss predominates* anhydremia causes renal failure and phosphate retention

The excessive administration of intravenous saline may cause an acidosis Sodium occurs in the plasma as the chloride and bicarbonate When fluid loss is restored with sodium chloride solution, the acidity of the plasma *becomes increased as the percentage* of bicarbonate decreases The excretion of an acid urine to remove the excess chloride is necessary to restore the bicarbonate

A reduction of base with a compensatory secondary CO_2 deficit is the third type of acidosis This type is uncommon but may occur in acute diarrhea when more salts than water are lost in the feces

Alkalosis Alkalosis is frequently due to a primary CO_2 deficit resulting from diminished *CO_2 production and/or increased* CO output The latter is the most common

Hyperventilation at rest washes out an excessive amount of CO_2 and lowers the CO_2 tension of arterial blood This sometimes occurs in hysteria, neurasthenia and other functional nervous disorders as well as in certain organic diseases of the nervous *system* which involve the region of the hypothalamus

Hyperpnea due to exposure to high temperatures *easily produces such an* alkalosis.

Anoxia at high altitudes, and more commonly in cardiac failure, often results in hyperventilation sufficient to induce an alkalosis

An acid deficit with the loss of acids stronger than carbonic and a compensatory secondary CO_2 excess also causes alkalosis

Possibly the commonest example of the above is the chloride deficit which occurs when HCl is lost into the stomach and *vomitus in high intestinal* or pyloric obstruction

Vomiting of any duration from various causes *usually leads to chloride* loss and alkalosis

An increase of base with secondary CO_2 excess is a common form of *alkalosis* particularly in the past with excessive alkali therapy in peptic ulcers It is still seen not only as a result of alkali therapy but *from* the common use of alkalis by the laity for "indigestion and acid stomach"

As emphasized above the therapy of acidosis and alkalosis in most cases is a question of dealing with the cause There are a few instances where direct therapy is indicated Acidosis due to primary CO_2 excess can be treated only indirectly and oxygen therapy is useful in a number of cases (e g congestive heart failure)

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pressed too far it is simply discontinued The retention acidosis of renal insufficiency is part of the picture of renal failure Uremia however does not consistently present an acidosis Emesis is common and acid loss from the stomach via this route may compensate for the retained acid anions and even cause an alkalosis

Uncontrolled diabetes and starvation frequently result in a ketone body acidosis (ketosis) Diabetic acidosis is controlled by the use of insulin and diet rarely with the use of alkali It is the result of the failure to store and use glucose normally so that a high level of fat metabolism ensues The ketone bodies are produced in the liver and carried elsewhere for combustion Being acid and stronger than bicarbonate they produce the second type of acidosis In starvation the ketosis occurs because of an absolute lack of glucose It is a physiologic mechanism which may have ill effects if of high intensity The starvation may result from vomiting diarrhea or failure to take food It is best treated with carbohydrate food in the form of intravenous glucose solution if necessary Alkali therapy if it is indicated at all should be used in babies or small children with ketosis 1000 cc of ⅙ molar sodium lactate solution by the intravenous route is preferred The lactate is metabolized and the effect is the same as administering sodium bicarbonate solution without the disadvantages of its instability As a rule alkali is unnecessary and normal saline will suffice to restore the fluid loss and overcome dehydration produced by acidosis

Alkalosis resulting from a primary CO deficit caused by hyperventilation may be controlled by having the subject rebreathe into a paper bag from time to time The chief use of this procedure is to aid the neurasthenic in controlling and understanding his symptoms As in all types of alkalosis the immediate problem is to prevent the tetany which occurs following a fall in the ionization of calcium as the pH of the plasma is raised

The alkalosis of intestinal obstruction is a secondary disturbance If surgery is not indicated immediately the loss of acid and base through the vomitus or into the gastrointestinal tract may often be controlled if no food or fluid of any kind is taken by mouth The restoration of the salt and water in any case is best done with ordinary saline solution administered intravenously Glucose is also useful because the lack of food dehydration and even the alkalosis may promote a ketosis A ketosis is not always an acidosis and if present from glucose lack may be enhanced by an alkalosis

Alkali therapy may cause a serious alkalosis Discontinuing the alkali is usually the only necessary step but on occasion renal failure supervenes and it is desirable to give small doses of ammonium chloride as an acidifying salt

EATON M MACKAY

CHAPTER IV

DISEASES OF THE GLANDS OF INTERNAL SECRETION

ADDISON'S DISEASE

With the newer methods of treatment the life of the patient with Addison's disease has been extended several years The improved outlook is a tribute to the many workers in the fields of biochemistry and clinical re search even though our treatment is mainly substitutive in type The treatment of patients requires an understanding of the pathologic physiology, for the use of the various therapeutic measures is governed by knowledge of the altered physiologic dis turbances

The important guides to adequate treat ment are clinical symptoms and progress, i e, weakness gastro intestinal symptoms, appetite changes in body weight, fluctuations of blood pressure pulse, and labora tory findings i e blood hematocrit readings, blood urea nitrogen, blood sugar determinations, and blood sodium determinations It must be re emphasized that though we have effective therapeutic agents they are not in ... ment therap

may be able to lead a normal existence, if not unduly subjected to stresses and strains, on simple dietary management including an increase in daily salt intake Such patients, however are potentially in danger of crisis ... the ... ing danger The clinician must always bear in mind that he is dealing with a chronic illness, which at any moment may become seriously acute He must present an under standing of the disease to the patient, but not in such a manner that a heavy burden is made more unbearable

Understanding of the life situation, the items in the patient's behavior which might be present that could not withstand added insult, must always be considered in presenting to the patient the management of his illness and what to watch for in symptoms The patient should be taught the stresses and strains which could precipitate symptoms of the disease overexertion in fections, exposure to marked changes in temperature, injuries, irregularity in food in take He should be taught the symptoms that are warning signs and to report to his phy sician questionable symptoms that he does not understand These should be taught as thoroughly to the patient as they are taught to the medical student in the classroom

In general it is advisable to teach the technic of intramuscular injections even though injections may not be needed at the time of instruction This will enable the pa tient to use the syringe and needle when necessary

DIETARY MANAGEMENT A diet adequate in calories to maintain optimal weight, high in protein and carbohydrate and low in fat which is given usually in three feedings and ... salt sho ll form the basis ... stein ... vail ... able foods, then protein can be administered in the form of powdered amino acids and protein hydrolysates given in milk and tomato juice

Although the use of low potassium diets (1 6 to 2 0 gm) has been advocated in the past at the Mayo clinic by Rynearson and his co workers, the availability of adrenal ... cortex ... tion such diets were once used Most patie found this restricted diet unpalatable and its method of preparation troublesome With the advent of desoxycorticosterone acetate

and the more potent adrenal cortical extracts patients report that they would prefer the daily hypodermic injection of hormones *rather than be restricted so markedly in their* food intake Most patients also report a sense of well being while on specific hormone therapy that they do not have on dietary management with increased salt intake The dangers of the decreased potassium diet while on desoxycorticosterone acetate will be discussed later

Increased Salt Intake The average American diet contains about 5 gm of NaCl per day In attempting to maintain the patient on salt alone it is necessary to add an additional 10 to 20 gm daily The simple statement to the patient that he should salt his food heavily is not a safe procedure for the quantity may fall short of what is needed to maintain a normal electrolytic pattern The salt is best prescribed in the form of enteric coated tablets taken several times during the day It must be kept in mind that nausea vomiting and diarrhea may be produced by excessive salt intake

Cortical Extract Adrenal cortical extract is usually taken intramuscularly or subcutaneously by the patient in doses of 2 to 5 cc usually divided into two doses during the day It is given at the time of crisis intravenously but its effectiveness by this route of administration is transitory In contrast to desoxycorticosterone acetate there is no danger of overdosage and never any danger of hypertension The use of this excellent preparation is limited because of expense Some patients need as much as 50 cc per day It is advisable to use increased salt with the use of cortical extract and thus cut down the amount of the latter necessary Whole extract has an effect on the hypotension indirectly by improving the patient generally

Whole adrenal cortical extract has an added feature in that it has an effect on carbohydrate metabolism Beef adrenal cortical extract has a relatively slight and transient effect on the blood sugar Pork adrenal cortical extract has a direct action on carbohydrate metabolism that is greater than beef adrenal cortical extract and tends to correct the blood sugar abnormalities of Addison s disease

Desoxycorticosterone Acetate (*Intramuscularly*) Satisfactory management of Addison s disease has been obtained by the *intramuscular injection of desoxycorticosterone acetate* It can be given subcutaneously but it is never given intravenously for it is put up in sesame oil The average dose is from 1 to 5 mg daily intramuscularly usually in one dose At times of stress the dose may be increased to as high as 25 mg per day but one must watch carefully for rapid gain in weight edema or rise in blood pressure There are some patients who need the injection every other day or every third day

Pellets Pellets are never inserted in the early stages of the management of Addison s disease During the first few months of treatment with synthetic hormone a gradual decrease in the patient s requirement of hormone usually ensues As the patient s clinical and electrolyte pattern improves the requirement decreases Usually the patient is treated for at least 3 months with intramuscular injections before pellets are inserted and then only when the intake of NaCl has been relatively constant for this period of time The use of pellets is economical and has the same effect as when the synthetic hormone is given intramuscularly The average duration of a pellet implant is from 10 to 13 months

The control of the hormone by this method is more difficult for if there is overdosage the patient will need surgical intervention It is wiser to implant less than necessary and supplement with intramuscular injections when necessary Patients over 40 are poor subjects for implantation for they have a tendency to increased blood pressure and angina Patients in this age group need more frequent readjustments of dosages than in the younger group

usually 60 to 75 per cent of that dosage required by injection Thus if a patient needs 5 mg of desoxycorticosterone acetate per day he would need to have 10 pellets inserted to get 3 0 mg per day

Implantation is a minor surgical procedure The pellets are implanted in the infrascapular region under local anesthesia with

a special trocar designed for this purpose

SUBLINGUALLY Desoxycorticosterone acetate in propylene glycol may be used sublingually The preparations usually employed contain 10 mg per cubic centimeter and are given in divided doses of 0 1 cc each The objections to this form of therapy are that three to five times as much of the synthetic hormone is needed when taken in this form as when taken by injection Sublingual desoxycorticosterone is needed several times during the day and must be kept sublingually for 5 minutes which some patients find difficult to do Moehlig reported swelling of the submaxillary glands following this method of administration

INTRA ORAL ADMINISTRATION Anderson and co workers have used intra oral administration of desoxycorticosterone acetate since 1940 Because the mixture of synthetic hormone used sublingually needed meticulous care in handling they employed as a solvent a polyethylene glycol wax of high molecular weight which was solid at body temperature A tablet containing 2 0 mg of hormone was placed inside the cheek The tablets slowly disappeared in an hour Fourteen patients with Addison s disease have been reported managed by this group with this form of therapy

Dangers and Disadvantages There is definite danger from overdosage with the synthetic hormone Hypertension pulmonary and peripheral edema and congestive heart failure have been reported with fatalities Muscular weakness and paralysis associated with fall in serum potassium are also known to occur when there has been a curtailment in the amount of potassium in the diet For this reason there should be no limitation of potassium intake in the diet when desoxycorticosterone acetate is used Forster and his associates have found some degenerative lesions in the cerebral arteries while other arteries studied have failed to reveal any changes in patients treated with the synthetic hormone Local irritation due to the sesame oil may be an annoying factor with intramuscular injection The treatment for overdosage is reduction in the size of the dosage of the hormone the withdrawal of NaCl and occasionally the administration of potassium salts usually 10 to 20 cc of a 10 per cent solution of potassium citrate which may be added to any palatable fruit drink

IMPLANTATION OF A GRAFT Broster and his co workers described a case in which a hypertrophied adrenal gland from a patient suffering from the adrenogenital syndrome was grafted by vascular anastomosis into a patient suffering with Addison s disease Fourteen months after operation the patient had been without substitution therapy for 7 weeks and had shown no symptoms of adrenal insufficiency This mode of treatment is certainly the ideal method Effort should be continually directed toward this more physiologic type of therapy

USE OF OTHER ENDOCRINE PRODUCTS Williams and his co workers made a study of 5 patients with Addison s disease with the objective of producing a clinical improvement superior to that obtained with desoxycorticosterone acetate alone particularly with regard to the patient s muscular strength Testosterone propionate improved the strength slightly to moderately However after the patient had worked a few hours he noticed more definite fatigue than normal The deficiency of the corticosterone is regarded as the probable cause of this fatigue

CORTISONE Thorne has recently advocated the use of 17 hydroxy 11 dihydrocorticosterone (cortisone) in patients with adrenal insufficiency Because of this hormone s ability to aid in the regulation of carbohydrate metabolism it is a valuable adjunct to therapy with desoxycorticosterone After careful regulation of the dosage of cortisone by administering 10 to 20 mg of cortisone in oil daily pellets of cortisone are implanted subcutaneously in a quantity calculated to release 10 to 20 mg of the hormone per day Reimplantation of cortisone pellets must be repeated every 2 to 3 months

The Management of Acute Adrenal Insufficiency The proper care of the patient with adrenal crisis embodies the understanding of the altered physiologic status and the use of our armamentarium of substitutive therapy The state of shock with the dehydration and circulatory collapse demands the immediate institution of emergency measures At once the patient must be started on 5 per cent glucose in saline intravenously with the concomitant adminis

tration of 50 to 100 cc of adrenal cortical extract intravenously At the same time the patient should be given 25 to 50 cc of adrenal cortical extract intramuscularly as well as 10 to 20 mg of desoxycorticosterone acetate intramuscularly Epinephrine both the aqueous and in oil may be used in combating the shock

The patient in adrenal crisis must have constant attendance Therapy does not end with the institution of the above measures but continues throughout the critical period by constant observations of the blood pressure pulse blood urea nitrogen blood sugar sodium and chloride determination The clinical status is observed most critically especially the lungs for signs of congestive failure for too much desoxycorticosterone acetate or too rapid an inflow of intravenous fluids may throw the patient into pulmonary edema

A continuous intravenous drip of 5 per cent glucose and saline is continued until the patient is able to take nourishment by mouth and all the gastro intestinal symptoms have subsided The amount of saline to be given can be determined only by observation of the patient It may be necessary to give whole adrenal cortex intravenously as often as every hour There is no danger from overdose of this preparation in contrast to the danger with desoxycorticosterone acetate The chief objection to the use of whole adrenal cortex is its costliness This should never be a consideration in so critical a picture When the tide of crisis has turned the intervals between dosages of whole adrenal cortex may be increased and the amount given may be gradually decreased

In contrast the amount of synthetic hormone given must be gauged most carefully Usually an interval of 10 to 12 hours may elapse between dosages of intramuscular desoxycorticosterone acetate Epinephrine is usually needed only at the onset of management of the shock picture Transfusion of whole blood or plasma may be used to combat the severe circulatory collapse

The change of management from the massive therapy as outlined above to a regimen designed for the maintenance of the patient in the normal routine of his life is a gradual one The ultimate goal is the use of substitutive therapy in the form most acceptable to the patient and his economic status which is always a factor with costly medications The change to the newer regimen can be guided only by the meticulous observation of the clinical and laboratory findings

The Management of Acute Infections in Addison s Disease Any infection is of grave importance in a patient with Addison s disease even a mild upper respiratory infection These patients notoriously have poor

patients report mild symptoms to their physician and immediately fortify themselves with an increase in salt intake and an increase of hormone by injection Antibiotics and chemotherapy are usually started earlier in these patients than is usual with other individuals

The Management of Surgical Conditions in Addison s Disease In spite of our armamentarium of substitutive therapy

period during which the patient should receive 25 to 50 cc of whole adrenal cortex per day given subcutaneously in divided dosage Desoxycorticosterone acetate in dosages from 5 to 15 mg may be given intramuscularly each day Every effort must be made

room in

and with

pattern

of crisis is ever present Just before surgery during the operation and immediately after the operation 25 to 50 cc of whole adrenal cortical extract should be given intravenously along with a constant intravenous drip of glucose and saline Spinal anesthesia should be avoided patients with Addison s disease tolerate inhalation anesthesia better Wherever possible local anesthesia should be used

The Management of Pregnancy in Addison s Disease The first trimester of pregnancy carries with it the danger of nausea and vomiting The inability to maintain adequate nutrition under these circumstances may precipitate a crisis It is well

then, to fortify the patient with multiple doses of whole adrenal cortical extract daily along with desoxycorticosterone acetate During the remaining trimesters there is constant need for supervision of the salt intake and desoxycorticosterone acetate dosage, for with the rise in circulating estrogen and progesterone, with their ability to help retain sodium in the body, plus whatever hormone comes from the fetus, there may be danger of hypertension and edema During the actual management of delivery, however, the patient should be treated as if in crisis This type of management should be kept up in the postpartum period and gradually the dosages of whole adrenal cortical extract and desoxycorticosterone acetate decreased until all danger has passed

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THYROID DISEASES

HYPERTHYROIDISM

The introduction in 1943 of new and potent antithyroid drugs did, for a time, tend to upset the standard and accepted methods of treating hyperthyroidism It was suggested by some and, of course, sincerely hoped for by those interested in hyperthyroidism, that these new substances would accomplish a medical cure for this disease and that the era of thyroidectomy was soon to pass Sufficient time has now elapsed and clinical trial of the new goitrogens has been sufficiently widespread to permit an understanding of their true value so that now again we can establish a practical plan for the therapy of hyperthyroidism Unfortunately, we may soon again be thrown into a state of confusion concerning therapy with *the advent of radioactive iodine* which at the present time is undergoing experimental study Because of the problems concerned

with the use of radioactive iodine and because of its potential dangers however it will be some time before the exact therapeutic place for this agent is established

A practical approach to the treatment of

that the diagnosis of hyperthyroidism be definitely established before treatment is begun and should there be any doubt it is preferable that the patient be given a period of observation since hyperthyroidism is not a static disease and if one waits sufficiently long the diagnosis usually becomes evident

Once the diagnosis of hyperthyroidism is established the next step deals with the decision as to the type of goiter present whether it is primary hyperthyroidism (exophthalmic goiter—diffuse hyperplasia) or adenomatous goiter with hyperthyroidism (toxic nodular goiter) This differentiation of hyperthyroidism is necessary since the response to treatment to be expected depends on the type of goiter For instance the symptoms of adenomatous goiters are rarely benefited by Lugol s solution whereas in primary hyperthyroidism improvement (rarely complete) can always be expected Ultimate and decisive treatment is advisable for adenomatous goiter and subtotal thyroidectomy is indicated whereas some patients with mild primary hyperthyroidism may obtain a cure or prolonged remission following treatment with iodine alone Again when the antithyroid drugs are used (thiouracil propylthiouracil methylthiouracil etc) it is found that a patient with primary hyperthyroidism responds more readily to a given dose than does a patient with adenomatous goiter with hyperthyroidism the latter requires about twice the time for reduction of an equally elevated basal metabolic rate to normal Therefore in discussing the treatment of hyperthyroidism a careful distinction will be made of the two types of the disease classified as primary hyperthyroidism (exophthalmic goiter) and adenomatous goiter with hyperthyroidism

Under *primary hyperthyroidism* are grouped (1) mild hyperthyroidism with slight thyroid enlargement (2) moderate to severe hyperthyroidism with definitely enlarged thyroid (3) recurrent hyperthyroidism (after thyroidectomy) and (4) relapsing hyperthyroidism after antithyroid (drug) treatment

treatment with Lugol s solution alone A daily dose (10 drops) of Lugol s solution accomplishes in a few weeks complete relief of symptoms and a return of the thyroid to normal size but with perhaps firmer consistency That this represents a cure of the hyperthyroidism is unlikely but many patients may remain symptom free for years This assumption is borne out by the history which hyperthyroid patients frequently reveal of similar complaints weight loss and nervousness which subsided after iodine treatment given years before Patients who are given iodine as the sole therapy must be advised that one cannot predict with certainty if the treatment will be immediately successful and if successful whether the thyroid overactivity will remain cured or recur at some time in the future Therefore when embarking on iodine therapy patients must be kept under observation and suitable steps must be taken if the hyperthyroidism is not completely controlled Complete control includes relief of all symptoms and return of the weight and the metabolic rate to normal If after 3 months of daily administration of iodine the patient is not well iodine therapy must be abandoned and more energetic treatment instituted since such a patient is no longer to be considered as having mild hyperthyroidism

Patients with mild hyperthyroidism can also be given a trial of treatment with the new antithyroid drugs Thiouracil in a daily dose of 600 mg or 300 mg of propylthiouracil daily should be continued until the basal metabolic rate reaches normal at which time the dose of medication should be halved Treatment should be continued and complete control maintained for a period of 3 to 6 months the dosage being further reduced if control seems satisfactory At the end of 3 to 6 months treatment is discontinued and the patient is observed every 1 to 2 months for possible relapse of hyperthyroidism This type of therapy is also trial treatment and patients must be aware of the

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with the use of radioactive iodine and be cause of its potential dangers however it will be some time before the exact thera peutic place for this agent is established

A practical approach to the treatment of a given case of hyperthyroidism is dependent on a number of factors which must be given sufficient consideration before proceeding with treatment It is of course essential that the diagnosis of hyperthyroidism be definitely established before treatment is begun and should there be any doubt, it is preferable that the patient be given a period of observation since hyperthyroidism is not a static disease and if one waits sufficiently long the diagnosis usually becomes evident

Once the diagnosis of hyperthyroidism is established the next step deals with the decision as to the type of goiter present whether it is primary hyperthyroidism (ex ophthalmic goiter—diffuse hyperplasia) or adenomatous goiter with hyperthyroidism (toxic nodular goiter) This differentiation of hyperthyroidism is necessary since the response to treatment to be expected de pends on the type of goiter For instance the symptoms of adenomatous goiters are rarely benefited by Lugol s solution whereas in primary hyperthyroidism improvement (rarely complete) can always be expected Ultimate and decisive treatment is advisable for adenomatous goiter and subtotal thyroi dectomy is indicated whereas some patients with mild primary hyperthyroidism may obtain a cure or prolonged remission follow ing treatment with iodine alone Again when the antithyroid drugs are used (thio

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Mild Hyperthyroidism An occasional patient with mild hyperthyroidism and only slight thyroid enlargement is amenable to treatment with Lugol s solution alone A daily dose (10 drops) of Lugol s solution accomplishes in a few weeks complete relief of symptoms and a return of the thyroid to normal size but with perhaps firmer consist ency That this represents a cure of the hyperthyroidism is unlikely but many patients may remain symptom free for years This assumption is borne out by the history which hyperthyroid patients frequently reveal of similar complaints weight loss and nervousness which subsided after iodine treatment given years before Patients who are given iodine as the sole therapy must be advised that one cannot predict with certainty if the treatment will be immedi ately successful and if successful whether the thyroid overactivity will remain cured or recur at some time in the future There fore when embarking on iodine therapy patients must be kept under observation and suitable steps must be taken if the hyper thyroidism is not completely controlled Complete control includes relief of all symp toms and return of the weight and the meta bolic rate to normal If after 3 months of daily administration of iodine the patient is not well iodine therapy must be aban doned and more energetic treatment insti tuted since such a patient is no longer to be considered as having mild hyperthyroidism

Patients with mild hyperthyroidism can also be given a trial of treatment with the new antithyroid drugs Thiouracil in a daily dose of 600 mg or 300 mg of propylthio uracil daily should be continued until the basal metabolic rate reaches normal at which time the dose of medication should be halved Treatment should be continued and complete control maintained for a period of 3 to 6 months the dosage being further reduced if control seems satisfactory At the end of 3 to 6 months treatment is discon tinued and the patient is observed every 1 to 2 months for possible relapse of hyper thyroidism This type of therapy is also trial treatment and patients must be aware of the

high possibility of failure Since these antithyroid drugs cannot be administered without possible danger observation every 2 to 3 weeks is necessary at which time leukocyte and differential blood counts are determined *Patients must be acquainted with the* type of reactions (fever sore throat and skin rash) which may develop following the use of these drugs and advised to notify the physician at once should any such untoward *sign or symptom develop*

[illegible]

thyroid drugs followed by a carefully executed *subtotal thyroidectomy This offers* the patient prompt and decisive treatment and cure with a minimum of risk and eliminates the great chance of failure which is inherent in using antithyroid drugs in this type of hyperthyroidism with the hope of inciting a remission of the disease The disadvantages of maintenance treatment with antithyroid drugs are real and will be given consideration later in this discussion

Once the diagnosis of moderate to severe primary hyperthyroidism is established and a thyroidectomy is deemed advisable a program of antithyroid treatment is planned The duration of treatment prior to thyroidectomy depends on factors such as the level of basal metabolic rate duration of hyperthyroidism previous iodine administration age *of the patient degree of physical depletion* and status of the cardiovascular system Experience in preparing some 1 900 hyperthyroid patients for thyroidectomy has revealed that the average patient with primary hyper*thyroidism* will obtain a daily drop of 1 per cent in the basal metabolic rate when receiving 600 mg of thiouracil or 200 to 300 mg of propylthiouracil or methylthiouracil a day The 300 mg dose of propylthiouracil or methylthiouracil is limited to those patients with large goiters Therefore if a patient has a basal metabolic rate of plus 50 one can predict that 7 *weeks of treatment* will be required to return the metabolic rate to within a normal range Previous administration of iodine will delay response to treatment and in these cases 2 or 3 weeks must *be added to the* prediction time In the presence of advanced age long standing disease or cardiovascular complications (to be discussed later) it is not enough to return the metabolic rate to normal but maintenance treatment with halving the dose of the antithyroid drug should be continued until normal compensation has been restored and operative risk avoided Some patients may require as long as 3 to 4 *months to accom*plish this end and some have been carried on maintenance treatment for as long as a year before it was thought safe to proceed with *the operation* In addition to the antithyroid drug which is administered in a divided dose at 8 A M and 8 P M the patient should be advised to follow a program of adequate rest which should depend on his general condi*tion At times a week or 10 days of bed rest* is necessary at the beginning of treatment since benefit is rarely noted from treatment before this time Patients are urged to take a diet which is high in carbohydrate and protein in an attempt to regain the weight which has been lost Feedings between meals are also advised Stimulants such as coffee tea and alcohol are discontinued and emphasis is given to avoidance of tobacco since smoking has been observed on many occasions to retard the expected recovery Patients with associated heart disease are given *the usual cardiac treatment with a main*tenance dose of digitalis Medication other than antithyroid drugs digitalis and occasionally vitamins should be avoided so that should any reactions occur one can be certain as to the offending agent Occasionally phenobarbital ¼ grain (15 mg) four times a day may be necessary at the beginning of treatment to control undue *nervousness and* to induce sleep

[illegible] of the [illegible]

therapy until myxedema develops since this clinical state causes an increase in the operative risk Patients with myxedema are sensitive to narcotics This sensitivity *results in* decrease in respiratory rate and cough reflex which in combination with the laryngeal edema of myxedema and that following thyroidectomy may *lead to serious respiratory complications and at times* tracheotomy becomes necessary Therefore should myxedema occur antithyroid treatment must be withdrawn and thyroidectomy *postponed* until euthyroidism is present

Experience with many patients receiving antithyroid drugs has revealed the occasional patient who, although she has a normal basal metabolic rate, has objective evidence of myxedema such as lid edema puffiness of the face, and an elevated blood cholesterol This development makes it necessary for the physician to be aware of the possibility of myxedema following administration of these drugs and to determine the blood cholesterol level for confirmation of the diagnosis

In addition to the antithyroid drugs preoperatively Lugol s solution must be given to bring about involution of the thyroid gland in preparation for thyroidectomy Suitable involution is obtained when iodine is given during the last 3 weeks of treatment in combination with the antithyroid drug Lugol s solution 10 drops is given once a

onset of treatment The rapid effect of iodine will usually lessen the thyrotoxicosis The iodine should be discontinued after 7 to 10 days and resumed again 3 weeks before thyroidectomy Since administering Lugol s solution after operation, immediately or for some months has not been proved to be of certain value we have not resorted to its use

It must be admitted that primary hyperthyroidism can be kept under complete control by an adequate daily dose of any of the available antithyroid drugs The maintenance dose of the antithyroid drug must be decided in each case by a program of trial and error, that is, by gradually reducing the daily dose to a point short of relapse of the hyperthyroidism Maintenance treatment does carry with it many valid disadvantages which must be considered when this type of therapy is undertaken Chief among these are the problems entailed in trying to keep any patient on prolonged medical treatment Patients discontinue treatment for any one of a number of reasons with resulting relapse of hyperthyroidism which many can ill afford particularly the older patients with associated heart disease The possibility of toxic reactions is always a hazard which must be considered and should agranulocytosis develop prompt treatment with penicillin is necessary to avoid a fatality

Recurrent Hyperthyroidism Recurrent hyperthyroidism (after subtotal thyroidectomy) must be handled individually, according to the circumstances existing in each case In the presence of mild hyperthyroidism with a small remnant or remnants, the daily administration of 10 drops of Lugol s solution frequently accomplishes full control of hyperthyroidism with disappearance of all symptoms return of the basal metabolism

little hope of control can be expected from continued or prolonged administration of iodine The procedure of choice in this situa

of administering the antithyroid drugs as suggested for preparing patients for initial thyroidectomy Whether these patients with recurrent primary hyperthyroidism will be found to be suitable for radioactive iodine therapy or deep roentgen therapy must be settled following further investigation A patient with tetany or cord paralysis would seem suitable for some plan of treatment other than surgery Maintenance treatment with antithyroid drugs may, of course, be used if the problems dealing with its administration are understood and accepted

Relapsing Hyperthyroidism Relapsing hyperthyroidism after antithyroid treatment is a common problem Although it was initially reported that antithyroid treatment especially if continued for 9 to 12 months, would give a chance of cure or a remission of hyperthyroidism it is now increasingly evident that this is not the case Our early reported experience with attempts to bring

agent The relapse occurred within an average period of 3 months and bore no relationship to the duration of administration of the antithyroid drug Most of these patients had primary hyperthyroidism with moderate to large goiters or recurrent primary hyperthyroidism with moderate sized

All of these patients required further therapy, 11 had surgical intervention and one received radioactive iodine Nine of the 21 patients obtained benefit from the antithyroid treatment which brought about a prolonged remission from the hyperthyroidism Six of these patients have now been followed for from 4 to 5 years Two patients had a relapse 4 years after stopping treatment of these one patient remains well by taking Lugol s solution and one patient has had a thyroidectomy

If a relapse occurs after a period of 3 to 6 months of maintenance of true euthyroidism on antithyroid treatment it is evident that decisive treatment is indicated In such a situation iodine is not likely to be of value maintenance treatment with antithyroid drugs may be carried out but the program of choice is recontrol of hyperthyroidism with antithyroid drugs and thyroidectomy

Adenomatous Goiter with Hyperthyroidism This is one type of hyperthyroidism in which preventive treatment is effective Although the danger of malignant disease in adenomatous goiter is real (6 to 12 per cent) sufficient stress has not been placed on the insidious onset of hyperthyroidism in patients who have had a recognized nontoxic adenomatous goiter for years However with the increasing age span more attention must be given to the prevention of hyperthyroidism in older patients by urging thyroidectomy in cases of nontoxic adenomatous goiter when operation can be done with complete safety

When hyperthyroidism develops—and it frequently is insidious in its onset and leads to advanced states of physical depletion and at times serious cardiac complications—the most successful plan of treatment is preparation with antithyroid drugs followed by a subtotal thyroidectomy Adenomatous goiter with hyperthyroidism is not amenable to control with Lugol s solution and maintenance treatment with antithyroid drugs is not recommended chiefly because of the danger of malignant disease developing in an adenomatous goiter

The plan of preoperative therapy consists of continuing antithyroid treatment until the ... ches normal and all thiouracil or methylthiouracil in a daily dose of 300 mg if continued sufficiently long will bring about a satisfactory result Experience with many hundreds of cases of adenomatous goiter with hyperthyroidism indicates that 2 days of treatment are required to reduce the basal metabolic rate 1 per cent With this general rule one can predict the time necessary to restore a patient to euthyroidism However more time should be taken for those patients with large goiters those in the older age group and those who show evidence of general debilitation from long standing disease or in whom complications exist In these the full dose of antithyroid drug should be continued until the basal metabolic rate reaches normal and then a maintenance dose two thirds of the original dose should be continued for months if necessary until the patient s general condition is considered safe for subtotal thyroidectomy At times it has taken as long as 12 months of preoperative preparation to accomplish the desired degree of improvement When cardiac conditions are present the usual cardiac measures with digitalization are carried out along with antithyroid treatment Patients with adenomatous goiter are not given iodine preoperatively as are patients with primary hyperthyroidism since increased vascularity does not result from antithyroid treatment in this type of goiter

General Problems of Antithyroid Administration In addition to administering a dose of antithyroid drug which will result in a fall in the basal metabolism to normal the problem of observing patients and acquainting them with the possibility of reactions to these medicines is of real importance if serious complications and deaths are to be avoided Thiouracil which has almost completely been displaced by propylthiouracil has a reaction incidence of 9 to 10 per cent the most serious of these is agranulocytosis which has caused deaths The other reactions such as dermatitis fever and swollen ... mportance but ... nt Pro ... of only ... is the ...

reports indicate and our experience sub

stantiates them that this substance has a reaction incidence similar to that of thiouracil with agranulocytosis developing with equal frequency Patients with agranulocytosis if observed early and treated vigorously with penicillin and perhaps streptomycin recover in approximately 8 days It is therefore essential that each patient receiving these potentially dangerous drugs be carefully observed

When a patient has a reaction to one antithyroid drug and further antithyroid treatment is necessary it may be possible to shift to another antithyroid drug and continue treatment We have shifted from thiouracil to propylthiouracil from propylthiouracil to thiouracil or methylthiouracil from methylthiouracil to propylthiouracil or thiouracil Multiple sensitivities were observed in one patient so that it was necessary to experiment with five antithyroid drugs before one was found which was tolerated When shifting to another antithyroid drug it is necessary to administer a small test dose (50 mg) to avoid a serious reaction should the patient prove to be fever or skin sensitive Continued vigilance is necessary even if a shift at first seems possible since serious blood reactions may suddenly take place soon after the shift is made

Patients have been observed who tolerated one antithyroid drug in decreasing dose for months and then had a reaction indicating that the duration of treatment or the size of the dose has no relation to the occurrence of a reaction Again patients have been observed who tolerated one antithyroid drug until treatment was discontinued or lapsed and a few months later had a recurrence of hyperthyroidism which required further antithyroid treatment They were then found to be sensitive to the drug which was initially well tolerated Thus there is evidence that patients may become sensitized to these drugs which is an important point in favor of employing them solely as preoperative agents

Thyroid Storm Thyroid crisis or storm is an acute and extremely serious clinical state which occasionally follows thyroidectomy however only in patients who are still hyperthyroid It may also develop in the event of acute infection in patients with more severe states of thyrotoxicosis This condition may rapidly (within 24 to 36 hours) lead to death through an acute hypermetabolic hyperthermic and neurocirculatory upheaval Since this condition is to be avoided it is essential that no patient with goiter be submitted to thyroidectomy until euthyroidism is accomplished by adequate antithyroid therapy Also it is not sufficient to reduce the basal metabolism only partially preoperatively as serious crisis reaction may occur even after thyroidectomy in the presence of only mild hyperthyroidism

Should thyroid crisis develop energetic treatment is necessary and every effort should be instituted at once for little time is available in a condition which usually runs its course in 36 hours The patient should be placed in an oxygen tent containing a high concentration of oxygen Restlessness must be controlled by adequate doses of morphine sulfate ¼ grain (15 mg) every 2 to 3 hours at times being necessary and occasionally intravenous morphine or pentothal is indicated Fluids must be given in amounts up to 3000 to 5000 cc in 24 hours by constant intravenous drip Five per cent glucose in distilled water is alternated with 5 per cent glucose in normal saline solution Lugol s solution is given daily by placing 30 drops in one of the intravenous infusions Nasal tube feedings permitting the administration of proteins and additional carbohydrates should also be instituted if fluids and foods are not taken by mouth Hyperthermia is controlled by local application of ice caps removal of blankets and I have used to advantage continuous gastric lavage with ice water The latter measure is continued and repeated to restore the temperature to normal

Since thyroid storm may be complicated by infection it is advisable that both penicillin and sulfa drugs be given 100 000 units of penicillin are placed in the initial intravenous infusion and then 50 000 units are given subcutaneously every 3 hours Sulfadiazine 6 gm is also added to the initial infusion and 1 gm every 4 hours thereafter Excess bronchial mucus is common in this condition In addition to encouraging the patient to cough and expectorate it may become necessary to aspirate the trachea by direct visualization or by bronchoscopy This maneuver may correct the accumulatio

mucus which would lead to pulmonary atelectasis

Thyrocardiac Disease The problem of the thyroid patient with complicating heart disease has been greatly simplified with the advent of the antithyroid drugs However, a plea must be made for the prevention or earlier diagnosis of this condition since if a patient with thyrocardiac disease is permitted to go untreated, irreversible cardiac damage may develop and death may occur before adequate antithyroid treatment can be employed or even in spite of antithyroid therapy Although much has been written urging the removal of adenomatous goiters before the onset of hyperthyroidism we continue to see many patients late in life with advanced thyrocardiac disease Of these at least 4 patients die yearly in congestive failure or as a result of embolic disease owing to auricular fibrillation before effective antithyroid treatment can be given Since the thyroid gland of a patient beyond 60 years of age, who develops primary hyperthyroidism is never large averaging 29 gm in weight in a recent study thyroid disease is frequently overlooked in the older age groups because the neck is not carefully examined and the possibility of hyperthyroidism is not considered Therefore it is essential that *hyperthyroidism be considered in older* patients who have cardiac symptoms in whom weight loss is a prominent symptom The earlier thyroid heart disease is diagnosed and treatment begun the less serious is the damage to the heart and the greater will be the ultimate heart reserve

Before the use of the new antithyroid drugs the operative mortality of thyroidectomy for patients having thyrocardiac disease was 6 6 per cent (1922 to 1941) and of 141 patients who underwent operation from 1937 to 1941 it was 11 3 per cent Because of the serious operative risk in these patients two stage procedures were necessary in 35 per cent of the cases In contrast to these figures we now have data on our experience with patients who received antithyroid (*thiouracil or propylthiouracil*) treatment preoperatively Of the first 1 000 patients so treated and who had subtotal thyroidectomy, there were 135 patients with thyrocardiac disease One postoperative death occurred and no patient required a two stage operation We have now prepared 1 860 hyperthyroid patients for thyroidectomy, 4 postoperative deaths occurred and all 4 were in patients who had thyrocardiac disease This indicates that in spite of the most careful preoperative management of the thyrocardiac patient there is still some surgical risk although it has been substantially reduced

The preoperative management of the thyrocardiac patient must be *individualized* Treatment must be prolonged since it does *not suffice merely to bring about* a euthyroid state preoperatively It is advisable to maintain a euthyroid state until full cardiac and visceral reserve has returned and only then is the patient ready for thyroidectomy To accomplish this ideal *preoperative state*

per cent of the patients with auricular fibrillation have a reversal to regular rhythm before thyroidectomy

Preoperative treatment of the thyrocardiac patient entails antithyroid as well as cardiac measures The antithyroid drug must be given in a daily dose (propylthiouracil 300 to 400 mg daily) sufficient to return the basal metabolic rate to normal Patients with *large goiters will require even larger doses*

Patients with increased heart rates or fibrillation without congestive failure are not *given digitalis until the basal metabolic rate* reaches a point near normal since digitalis is of little therapeutic value when hyperthyroidism is still present *Patients with congestive heart failure* received combined therapy, cardiac and antithyroid The cardiac meas

drugs are begun simultaneously with the cardiac measures Patients usually become ambulatory in about 10 days by which time peripheral and pulmonary edema is relieved Combined treatment is continued until the *patient s general condition seems* suitable for safe thyroidectomy If the basal metabolic

rate is normal and heart reserve re established, the risk of thyroidectomy is minimal

Roentgen Therapy in the Treatment of Hyperthyroidism Roentgen irradiation of the thyroid in hyperthyroidism has as its purpose the decrease in the production of excess thyroid hormone This, of course, must be accomplished without serious dam

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should not be treated by irradiation since the occurrence of carcinoma in discrete nodular and even in multiple colloid adenomatous goiter is sufficiently high to warrant surgical intervention Therefore x ray irradiation should be limited to primary hyperthyroidism Even this use needs clarification since in our opinion thyroidectomy is the safest and most decisive way of treating primary hyperthyroidism In practice it has been our policy to limit roentgen therapy to patients with recurrent hyperthyroidism in whom various reasons such as the presence of tetany, recurrent laryngeal paralysis, or previous multiple operations, further thyroid surgery seems inadvisable Previous administration of Lugol's solution or the new antithyroid drugs does not contraindicate irradiation

Roentgen therapy is given in so called series The factors used in irradiating the thyroid gland are 200 kv platinum 20 ma 2 mm of copper and 1 mm of aluminum filtration and 50 cm target skin distance The cone used varies with each patient it should be sufficiently large to cover the gland with irradiation applied through a single anterior or lateral field An air dose of 300 r is given daily for 6 consecutive days until a total of 1800 r is given In 2 months if the patient has not reached a euthyroid state a second series of treatment is given On occasion three series may be necessary If little response follows the first or second series, it is not likely that roentgen therapy is the treatment of choice in the given case

Complications such as radiation sickness, transient sore throat erythema of the skin, tracheitis, and esophagitis occasionally occur The use of heavy filtration and small portals is essential to decrease the chance of permanent skin changes

It is difficult to determine from the litera

perience at the Lahey Clinic with patients who have recurrent primary hyperthyroidism has been reviewed by Hare and Salzman and includes 20 such patients in whom the follow up period after irradiation averaged 7 years The results in these 20 patients were considered good in 18, as interpreted by

Two patients were listed as obtaining poor results

It is obvious that an insufficient number

roidism in whom further thyroid surgical intervention is deemed inadvisable it is worthy of trial and may be met with satisfactory results

Radioactive Iodine Experience with this potent antithyroid agent has demonstrated its effectiveness in controlling hyperthyroidism It has not, however, received sufficient clinical trial so that either proper dosage or potential dangers have been fully determined As yet its use must be strictly limited to research centers where the problems of radioactive isotopes are undergoing controlled investigation The problems of handling and dispensing radioactive material, protection of workers against harm, and many other difficulties are still to be surmounted

avid for iodine, the radioactive substance is concentrated in the thyroid for concerted action on this gland Initial experiments on rabbits demonstrated that 30 or 40 days after a subcutaneous injection of I^{131}, fibrosis was present in the thyroid gland and a 50 per cent decrease in size of the thyroid was noted It is this action of destroying thyroid tissue which is purposely utilized when radioactive iodine is administered to human beings with hyperthyroidism Difference of opinion exists as to how radioactive iodine is

to be given—in one dose or divided small doses—and how to determine the required dosage to destroy just sufficient thyroid tissue to control the hyperthyroidism and still not induce myxedema Again, no definite opinion has been reached as to which type of patient with hyperthyroidism is best suited for this form of therapy, that is, should age be a deciding factor, should size limit its use, and many other still unanswered essential questions

Although there are 11 known isotopes of iodine, only two have been used in therapy, I^{130}, the 12 6 hour isotope and I^{131}, the 8 day isotope Both of these radioactive isotopes of iodine emit beta and gamma rays but with different energies and at different rates The average energy per disintegration of the beta rays expressed in million electron volts, is 0 270 for I^{130} and 0.205 for I^{131}, the ... 97 per cent ... hereas the ... The thyroid tissue absorbs about 90 per cent of the beta rays but the gamma rays pass through several centimeters of tissue with little absorption and their therapeutic effects are negligible Because of their penetrability, however, they may be used to measure uptake in the gland by suitable standardized Geiger counters

Tracer studies using from 50 to 75 microcuries of I^{131} show a variation in the uptake of iodine in various thyroid states In a normal gland 15 to 30 per cent of the dose is absorbed in 24 hours, in hyperthyroidism, 44 to 76 per cent, and in myxedema 1 to 4 per cent This uptake is inhibited by previous administration of iodine, such as Lugol's solution, iodized salt, or iodine present in dye used in cholecystography or intravenous pyelography

The employment of radioactive isotopes as therapeutic agents requires that the radiation dosage be determined At the present time determination of the proper dose represents the chief problem in utilizing radioactive isotopes, particularly because of difficulty in estimating properly the size of the gland to be treated This has led toward the plan of repeated small doses instead of a single large dose in attempting to destroy the thyroid gland The cases reported were given from 4 to as high as 77 millicuries of radioactive iodine by mouth in an effort to bring about the desired effect

The general trend of recovery from hyperthyroidism by radioactive treatment is reputed to require about 2 to 3 months and in some cases reported the thyroid gland had returned to an impalpable state Failures occurred chiefly in patients with high basal metabolic rates

Certain complications have been reported to follow radioiodine treatment Reactions such as thyroid storm have followed the use of what was later thought to be an excessive dose Transient and fixed myxedemas have been noted, the latter in about 12 per cent of the patients treated Sore throat and cough, lasting for a few weeks, have been reported Amenorrhea and anemia have also been reputed to occur Larger series must be treated and carefully followed for at least 5 to 10 years before all the possible reactions to this method of treatment will be known

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HYPOTHYROIDISM

The term hypothyroidism may have various interpretations but its use should be strictly limited to cases in which there is unquestioned clinical evidence of thyroid deficiency Patients with only lowered basal metabolic rates should not be included since it is well recognized that the range of the normal metabolic rate is wide and there are instances of patients with metabolic rates as low as —30 per cent who do not have the

slightest clinical evidence of thyroid deficiency These patients should not be included in the group with hypothyroidism since they are not benefited by thyroid treatment

Cases to be included in the classification of hypothyroidism must satisfy the following four criteria (1) reduced basal metabolic rate, (2) elevated blood cholesterol (myxedema with normal cholesterol does occur occasionally), (3) objective manifestations of thyroid deficiency and (4) unquestioned benefit must result from administering thyroid Should the first three diagnostic requirements be met, one can with certainty predict a change of these criteria toward normal following the administration of thyroid therapy

Classification of Hypothyroidism

(1) Cretinism with thyroid deficiency
(2) Childhood myxedema (spontaneous)
(3) Adult myxedema (spontaneous)
(4) Post thyroiditis myxedema
(5) Postoperative myxedema

Cretinism with Thyroid Deficiency Early recognition is essential for the successful treatment of cretinism since even adequate treatment when given late produces disappointing results Therefore, therapy should be started within the first months of life during which time the important brain centers are undergoing development A maintenance dose of U S P thyroid which will establish normal body growth should be given During the first 4 months of life, 1/10 grain, during the second 4 months 2/10 grain, and from 8 months to 12 months, 3/10 [illegible]

the patient reaches the age of twelve at which time the dose is 1 grain daily After sixteen years of age the daily maintenance dose should be 1½ grains When embarking on treatment for established cretinism the family must be advised that thyroid is a requirement for normal body growth and that under no circumstance should treatment be altered or discontinued A schedule of dosage should be carefully outlined with instructions regarding the type of thyroid to be given, and a prescription for the thyroid written in duplicate, permitting the druggist to refill it when necessary. Failure to instruct the family properly regarding future treatment leads to poor management which results in faulty physical and mental development

Should cretinism be discovered late in childhood, the initial dose of thyroid should be twice the suggested dose for that age A large dose of thyroid is given in the hope of forcing growth at a rate more rapid than normal One should not, however, expect complete restoration to normal when treatment is started late Should a cretin reach adult life without receiving thyroid, no improvement in mentality or growth will result from therapy

At or shortly after birth, congenital cretins are occasionally noted to have adenomatous goiters These goiters may alter the clinical course of the thyroid deficiency since as they increase in size there is gradual production of thyroid hormone which leads to lessening of thyroid deficiency Clinical improvement may continue until euthyroidism results, should excess thyroid hormone be produced, typical hyperthyroidism results This improvement in thyroid deficiency which may occur in cretins with goiters necessitates gradual reduction of the maintenance dose of thyroid Should hyperthyroidism actually develop, thyroidectomy is necessary After thyroidectomy, careful observation must be continued since thyroid deficiency may again develop so that administration of supplementary thyroid again becomes necessary

Childhood Spontaneous Myxedema. Children who are normal at birth, grow and develop normally, and then become thyroid deficient are considered to have childhood myxedema The diagnosis of this condition is frequently delayed since the pallor, edema of the face, and retarded growth are frequently thought to be caused by anemia or renal disease The absence of demonstrable renal disease, the presence of an elevated blood cholesterol, and roentgenologic evidence of retarded bone age aid in confirming the diagnosis of thyroid deficiency

The treatment of these children with thyroid results in prompt improvement in the [illegible]

normal level Between the ages [illegible]

years, U S P thyroid in a dose of ½ grain *usually suffices* as *does* ¾ grain from the age of 4 to 12 years The dose of thyroid may be safely increased by an additional ¼ grain in an attempt to incite a slightly more rapid bone growth than normal so that the patient may recover that which was lost during the period of thyroid deficiency In addition to the blood cholesterol level another excellent guide to the therapeutic response is the change noted in the bone age as determined by comparative roentgenograms of the hands Basal metabolic rates *are rarely neces*sary for judging therapeutic response Continued observation of these children is *advisable so that the dose of thyroid may* be altered with increase in age Here also the family should be acquainted with the future need for treatment with thyroid to obtain proper mental and physical development

Adult Spontaneous Myxedema The treatment of myxedema in adults should be divided into the management of patients less than 45 or 50 years and of those over 50 years of age This division according to age is extremely important since patients in the older age group must be given cautious treatment if serious cardiac complications are to be avoided The younger patients tol*erate sizable doses of thyroid with safety* and many standard textbooks advise starting treatment of all patients who have myxedema *with doses as large as 3 grains daily* Even in the younger patients this dose seems in excess and it is preferable for the initial *dose to be only* ½ *grain daily After 6 weeks* to 2 months of treatment on this dosage (½ grain daily) the patient should be studied again and a decision reached as to the future maintenance dose In most instances 1 grain of thyroid daily restores the patient to good health, with the *basal metabolic rate* and blood cholesterol level returning to normal A daily dose of U S P thyroid in excess of 1½ grains is never necessary to accomplish satisfactory euthyroidism

Older patients with spontaneous myxedema require cautious administration of thyroid These patients frequently have associated heart disease and many have had long standing myxedema which leads to hypercholesterolemia with resulting coronary sclerosis *Therefore, they must* be given only a small initial dose of thyroid and the longer the duration of myxedema, the smaller the initial dose Should the patient have symptoms of angina, *extreme caution* will be necessary The initial dose of thyroid in the older patients should never be over ¼ grain daily and should the patient have suggestive *cardiac symptoms* it should not exceed 1/10 grain a day

Older patients must be carefully observed and advised *that if any cardiac symptoms* develop or if those present become aggravated, the administration of thyroid must be *discontinued and* started again in smaller doses If at the end of one month the initial dose of thyroid is tolerated, it may then be *slowly* increased Monthly observations are continued until an adequate maintenance dose of thyroid is reached, which should rarely exceed 1 grain a day Many patients tolerate only a small dose of thyroid because of troublesome angina when larger doses are given The clinical improvement, however, from a dose of thyroid as small as 1/10 grain a day is at times considerable Angina may improve following the institution of thyroid treatment but this is not common should it occur, the dose of thyroid may be cautiously increased

Post thyroiditis Myxedema Seven per *cent of medical cases* with thyroiditis and 50 per cent of patients with thyroiditis which required surgery developed myxedema [illegible]

*dose of thyroid required for satisfactory con*trol is usually small varying *from* ½ *to* 1 grain a day The dose must, however, be individualized and an attempt made *to ac*complish control as determined by the patient s symptoms, the basal metabolic rate and the level of the blood cholesterol *Cau*tion must be followed in treating older patients

Postoperative Myxedema Myxedema *fol lows* subtotal thyroidectomy in approximately 2 5 per cent of cases Should microscopic study of the removed thyroid tissue show strumitis, the likelihood of myxedema developing is increased so that careful observation during a 3 to 6 month postoperative period is advisable Postoperative myxedema may at times be so transient that treatment is not indicated, but if it continues

beyond a 3 month period, therapy becomes necessary If treatment becomes necessary, it does not follow that it must be continued indefinitely, therefore, treatment should be withdrawn after a period of 6 to 9 months to determine with certainty if it is necessary The dose of thyroid should be the smallest possible to accomplish full control, and older patients should be cautiously treated

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THYROIDITIS

The treatment of thyroiditis is determined by an understanding of the nature of the pathologic process which is involving the thyroid gland Therefore, before instituting any type of therapy consideration should be given to determining the basis of the thyroid involvement Many times this knowledge can be obtained only by biopsy study or culture, which procedure may be combined with specific therapeutic or ameliorative measures

Acute Thyroiditis Acute thyroiditis may be nonsuppurative or suppurative with definite abscess formation Any one of a large number of organisms may be responsible for this condition Among these are such bacteria as the streptococcus, staphylococcus, pneumococcus, *Bacillus coli*, or anaerobic organisms, and even virus infections are probably responsible at times

This acute type of thyroid involvement is treated symptomatically by the local application of cold compresses or ice packs, and aspirin, 0 6 gm, or codeine, 30 mg, is given for relief of pain Trial treatment with antibiotic drugs, sulfonamides, penicillin, or streptomycin, given singly or in combination, should be carried out Should the specific offending organism be known, more intelligent antibiotic therapy can be used Should calization of the abscess or infection to one lobe

Thiouracil has been reported as being beneficial for the treatment of acute thyroiditis The first report, by King and Rosellim, indicated that 8 of 11 patients were promptly cured In all 8 patients the process was 3 weeks or less in duration and all were symptom free in one week, with complete disappearance of the thyroid enlargement Three patients did not respond to the drug The 2 cases reported by Cantwell obtained benefit in 48 hours One of the 2 patients did not respond to treatment with penicillin and sulfadiazine Thiouracil was administered in a daily dose of 600 mg, 200 mg three times a day That thiouracil is not specific for acute thyroiditis is indicated by personal experience with 2 patients who had identical thyroiditis, one responded promptly and in one patient the disease ran its usual course, starting in one lobe and proceeding to the other lobe in spite of continuous thiouracil treatment At the 1948 meeting of the American Goiter Association in Toronto Dr King reported continued success with the use of thiouracil in thyroiditis, however, similar results did not follow the use of propylthiouracil

Chronic Thyroiditis Chronic thyroiditis includes those conditions which the pathologists have differentiated as nonspecific thyroiditis, Riedel's struma, Hashimoto's struma, infectious granuloma, which includes syphilis, and tuberculosis and amyloidosis of the thyroid The first three types of thyroiditis include most of the cases of thyroiditis with Hashimoto s struma making up 40 per cent of cases, nonspecific thyroiditis 35 per cent, and Riedel's struma 25 per cent Although the diagnosis of chronic thyroiditis can be made with reasonable certainty, it must be differentiated from carcinoma Therefore, biopsy is indicated in any case in which there is any possible doubt as to the diagnosis That the diagnosis of thyroiditis is not considered sufficiently often is indicated by a recent report (Marshall). Of 187 cases of thyroiditis proved by biopsy, the correct diagnosis was considered preoperatively in only 25 per cent of the cases

Many patients with chronic thyroiditis do not require any type of treatment, but should pressure symptoms develop the choice of therapy is surgery In addition to securing definite information as to the pathologic process in the thyroid gland, relief of pressure on the trachea is accomplished by removing a wedge shaped piece of thyroid which should include the isthmus and medial portions of the lobes overlying the trachea The prethyroid muscles are then sutured to the tracheal fascia to prevent the thyroid lobes from becoming adherent to each other with return of pressure on the trachea In nonspecific thyroiditis this procedure may be all that is necessary, however, in Riedel s struma, in which the thyroid is adherent to all the surrounding structures there may be sufficient edema and even involvement of the recurrent nerve to make tracheotomy necessary Only the smallest amount of thyroid tissue necessary to relieve tracheal obstruction should be removed so as to avoid injury to the recurrent laryngeal nerves, injury to or removal of parathyroid glands, or an increased incidence of myxedema Even so postoperative myxedema, requiring treatment develops in 80 per cent of patients with thyroiditis who undergo conservative surgical procedures on the thyroid gland Should myxedema develop maintenance treatment with desiccated thyroid is indicated, using doses of thyroid adequate to return the basal metabolic rate and cholesterol level to normal In most patients who develop myxedema desiccated thyroid must be taken indefinitely Tetany is a rare development

Roentgen irradiation of the thyroid has been suggested for the treatment of thyroiditis and some favorable results are reported in the literature The additional fibrosis resulting from the reaction of irradiation may increase the constriction on the trachea and also further destroy remaining normal thyroid tissue, leading to myxedema

Tuberculous thyroiditis which is extremely rare can be diagnosed only by biopsy and pathologically it is usually of the miliary type Satisfactory results usually result from roentgen therapy

Luetic thyroiditis, which is also rare, may occur during secondary syphilitic manifestations or may be gummatous in nature The diagnosis is usually made by biopsy Antisyphilitic treatment results in prompt disappearance of the thyroid enlargement

ELMER C BARTELS

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THE PARATHYROID GLANDS

The parathyroid glands are subject to a variety of diseases which usually produce some alteration in the function of the glands Regardless of whether hyperfunction or hypofunction follows the pathologic process, the disturbances in calcium and phosphorus metabolism which accompany the change in function play a dominant role in producing symptoms and in determining treatment

Hypoparathyroidism PHYSIOLOGIC CONSIDERATIONS Hypoparathyroidism is most commonly caused by the accidental removal of the parathyroid glands or interference with their blood supply during operation on the thyroid It may also follow removal of a parathyroid adenoma More rarely, it occurs spontaneously as a chronic idiopathic variety without known cause Moniliasis has been associated with some of the spontaneous cases and has been considered as a possible etiologic factor Other reported causes include acute infections such as measles and influenza, chronic inflammatory changes such as tuberculosis and syphilis, and radiation injury

Parathyroid insufficiency which follows surgery on the thyroid or parathyroid glands usually occurs within 24 to 48 hours after the operation The onset is acute and the symptoms consist of excitability, anxiety, numbness and paresthesias of the lips and hands, carpopedal spasm, occasionally laryngeal spasm, and sometimes convulsions In some individuals the symptoms are so severe as to demand immediate and effective treatment In contrast to this, chronic parathyroid insufficiency has an insidious onset and may exist for a long time before it is recognized It produces a variety of symptoms including

paresthesias, mental depression, periodic attacks of tetany with or without convulsions, and finally cataracts and trophic changes in the nails and hair

[illegible] tion in the amount of circulating parathyroid hormone The lack of the hormone produces a fall in the calcium content of the blood serum, a decrease in the urinary excretion of phosphates and calcium, and an accumulation of phosphate in the blood serum, in addition, it causes a decrease in the normal activity of the osteoclasts The serum calcium usually falls below 7 mg per 100 cc, and the serum phosphorus rises to 5 or 6 mg per 100 cc, although in some cases it has increased to as much as 16 mg per 100 cc The low serum calcium content is responsible for the increased neuromuscular excitability, tetany, cataracts, and trophic changes The diagnosis of hypoparathyroidism is confirmed by the presence of a low serum calcium, a high serum phosphorus, and absence of, or greatly decreased, calcium in the urine in association with signs of tetany Renal insufficiency should be excluded since it may be responsible for changes in the levels of serum calcium and phosphorus which are similar to those of parathyroid insufficiency

The treatment of hypoparathyroidism has as its goal the relief of symptoms and the restoration of serum calcium to normal levels Inadequate treatment and its associated subnormal serum calcium levels may eventually be followed by the development of cata- [illegible]

[illegible] be completely controlled by the use of calcium and vitamin D or dihydrotachysterol The use of parathyroid hormone is rarely necessary except in the treatment of acute tetany where it is highly effective The choice of medication is dependent on the acuteness and severity of the parathyroid insufficiency as well as the individual variation in the response to each medication

ACUTE HYPOPARATHYROIDISM The treatment of acute hypoparathyroid tetany consists mainly in the administration of large doses of calcium orally, supplemented by occasional parenteral injections Treatment is initiated by the intravenous administration of 10 to 20 cc of a 10 per cent solution of calcium gluconate This may be repeated at intervals of every few hours if needed In severe tetany a constant intravenous drip of calcium gluconate may be used This preparation may also be given intramuscularly if necessary Calcium chloride (5 per cent solution) may be used in place of calcium gluconate and in the same dose It must never be given intramuscularly, and great care must be used to avoid any spillage outside the vein since such extravasation will produce a slough Furthermore, venous thrombosis at the site of the injection sometimes follows its use All calcium preparations given intravenously should be injected slowly to avoid unpleasant flushing, nausea, vomiting and fall in blood pres[illegible]

[illegible] ling the [illegible] calcium [illegible] in the powdered form has proved to be satisfactory and is usually well tolerated by the patient It is administered in doses of 4 gm every 2 hours until numbness and tingling have subsided Each 4 gm dose is dissolved in hot water and then flavored with some palatable liquid Canned orange juice is satisfactory, although other fruit juices, tomato juice, or tea may be substituted When the acute symptoms of tetany have been relieved, the patient is placed on a maintenance dose of calcium lactate of 1 or 2 heaping teaspoonfuls (4 to 8 gm) three or four times a day Calcium chloride, which may be substituted for calcium lactate, is readily soluble in water, provides a high percentage of available calcium, and is well absorbed from the gastro intestinal tract Its chief drawbacks are its astringent action in the mouth and its [illegible]

[illegible] juice

The chief indication for the use of parathyroid hormone is in the treatment of those patients with acute tetany who cannot take sufficient calcium by mouth, either because of inability to swallow or because [illegible] nausea and vomiting The [illegible] patient over the critical [illegible]

take an adequate dosage of calcium and vitamin D or dihydrotachysterol orally. Parathormone causes a lowering of the serum phosphorus level by producing a phosphate diuresis, and an increase in the serum calcium level by stimulation of the osteoclasts. The maximal effect of parathyroid hormone is reached in 8 to 24 hours, with a peak at about 15 hours. It is given initially in a dose of 50 to 100 units intramuscularly and repeated in 12 hours if necessary. Thereafter *10 to 20 units may be given daily until treatment* with calcium and an activated sterol becomes effective. Frequent determinations of the serum calcium level should be made in order to control the dose properly. Prolonged treatment with the hormone is unnecessary since other measures are completely successful in controlling even severe cases. In addition, frequent injections over a long period might lead to the development of antihormones which necessitate the administration of larger and larger doses in order that the desired effects may be achieved.

Additional measures are sometimes necessary in the treatment of acute tetany. The intake of milk in the diet should be restricted because of its high phosphate content. A high intake of phosphate is capable of precipitating tetany, for with a rise in the serum phosphorus level the serum calcium level may be further depressed, thus favoring the appearance of tetany (*Jones*).

Severe laryngeal spasm in rare cases may require laryngeal intubation or even tracheotomy. Paralysis of one vocal cord in association with tetany predisposes to the development of laryngeal spasm.

Chronic Hypoparathyroidism. The severity of the tetany and its response to calcium therapy will indicate the degree of parathyroid insufficiency and the need for further treatment. Tetany which follows thyroid surgery may disappear spontaneously within a few days as the edema in the tissues of the neck subsides or within 2 or 3 months as the remaining parathyroid glands hypertrophy. More rarely, it is permanent, requiring prolonged maintenance treatment. Mild cases of tetany are sometimes fully controlled by calcium therapy alone. More often the use of calcium in combination with one of the activated sterols is necessary.

Calcium lactate is administered orally in doses of 1 or 2 heaping teaspoonfuls three or four times daily. The total daily dose may be prepared each morning and divided into four or five equal portions to be taken at properly spaced intervals through the day. To facilitate absorption from the gastrointestinal tract, each dose should be taken before meals.

The activated sterols play an important role in the management of chronic parathyroid insufficiency (*McLean*). *Calciferol* (vitamin D_2) and dihydrotachysterol (A.T. 10) are two irradiation products of ergosterol which possess the same actions of increasing

excretion than on calcium absorption. Its action resembles that of parathyroid hormone more closely than does the action of vitamin D and for this reason would seem to be the ideal drug. Vitamin D has a greater effect on calcium absorption than on phosphate excretion. It has a slower action than A.T. 10 but its effect on the serum calcium level is more prolonged. The results of treatment with vitamin D have been highly satisfactory. Since it is less expensive than A.T. 10, it is usually prescribed first.

Calciferol (vitamin D_2) is available in pure crystalline form and is dispensed in capsules containing 50,000 international units each. One milligram of calciferol is equivalent to 40,000 international units. Di[illegible] lable in an oily solu[illegible]

in capsules each containing 0.625 mg. of the crystalline sterol and 2 capsules are equivalent to 1 cc. On the basis of comparative studies both in animals and human beings, 1 cc. of dihydrotachysterol (containing 1.25 mg. of the crystalline substance) is equivalent to about 10 mg. of calciferol or 400,000 international units.

The plan of treatment with the activated sterols is to give large initial doses until the serum calcium is near the normal level and then to reduce it to small daily maintenance doses. The initial dose of dihydrotachysterol is 2 to 3 cc. (4 to 6 capsules) per day until the serum calcium is normal. It is then re-

duced to about 2 to 5 cc per week A corresponding initial dose of calciferol would be 800 000 to 1,200 000 units daily, however, it is rarely necessary to give as large an amount as this since adequate effect usually can be obtained with 300 000 to 800,000 units daily The maintenance dose of calciferol varies between 50,000 and 200 000 units per day Calcium should always be given with the activated sterols

Treatment is controlled by observing the patient's response by periodic determina tions of serum calcium and occasionally by the use of the urinary Sulkowitch test In sufficient treatment is associated with such

sterols is quite quickly apparent to the patient because of headache, nausea, vomiting, and an intense dislike or aversion to calcium (Hurxthal and Claiborne) Medication is often discontinued by the patient himself be

of these reactions In contrast patients with conditions other than tetany who are receiv ing a high dosage of vitamin D may experience prolonged intoxication without being aware of it It is in such cases that kidney damage and metastatic calcification are most likely to occur

Periodic determinations of the serum calcium provide the most reliable control of therapy The urinary Sulkowitch test has been recommended (Albright et al) also as a guide to treatment The test is a rough quantitative measure of the urinary excretion of calcium It is performed by adding 5 cc of urine to 5 cc of Sulkowitch reagent If no precipitate is formed the urine is free of calcium and the serum calcium is below the renal threshold of about 7 5 mg per 100 cc If a fine precipitate is formed the serum calcium is between 8 and 10 mg per 100 cc A heavy white cloud indicates a serum calcium level above 11 mg per 100 cc The test has its greatest usefulness during the initial treatment of tetany before the serum calcium has reached normal levels A negative Sulkowitch test indicates that the dosage of activated sterol is inadequate When the test becomes consistently positive it is safer to rely on serum calcium determinations

Supplementary measures may be prescribed but are only rarely necessary Low phosphate diets have been recommended on sound theoretical grounds, but are difficult to follow Restriction of the intake of milk is advisable in all cases The use of amphojel (120 to 160 cc per day) has been advocated as a means of reducing the absorption of phosphates from the intestinal tract, but this is usually unnecessary Acidifying salts such as ammonium chloride may be useful for the treatment of tetany resulting from alkalosis, but they have no place in the management of hypoparathyroidism Desiccated thyroid should be prescribed only if an associated thyroid deficiency is present It may be of incidental help in the mobilization of cal cium but this is of minor importance and not an indication for its use

With proper management, patients with hypoparathyroidism can be kept in a perfectly normal physical and chemical state If cataracts have already formed prior to the institution of treatment, the maintenance of a normal blood calcium inhibits their further growth but will not cause them to disappear Careful supervision of the patient, however, is necessary in order to secure the best results

Primary Hyperparathyroidism Primary hyperparathyroidism is a condition resulting from excessive production of the parathyroid hormone, which in turn causes marked changes in the metabolism of calcium and phosphorus Most of the cases (86 per cent) are caused by a hyperfunctioning parathy roid adenoma, and about 14 per cent of cases

pal actions that of increasing the urinary excretion of phosphorus, and that of increas ing the activity of the osteoclasts As a result, there is a decrease in the level of serum phosphorus, an increase in the level of serum calcium, an increase in the urinary excretion of calcium and phosphorus, and demineralization of bones

The symptoms are the result of these physiologic changes Hypercalcemia is respon sible for muscular weakness and atony, constipation, loss of appetite, loss of weight,

take an adequate dosage of calcium and vitamin D or dihydrotachysterol orally Parathormone causes a lowering of the serum phosphorus level by producing a phosphate diuresis and an increase in the serum calcium level by stimulation of the osteoclasts The maximal effect of parathyroid hormone is reached in 8 to 24 hours with a peak at about 15 hours It is given initially in a dose of 50 to 100 units intramuscularly and repeated in 12 hours if necessary Thereafter 10 to 20 units may be given daily until treatment with calcium and an activated sterol becomes effective Frequent determinations of the serum calcium level should be made in order to control the dose properly Prolonged treatment with the hormone is unnecessary since other measures are completely successful in controlling even severe cases In addition frequent injections over a long period might lead to the development of antihormones which necessitate the administration of larger and larger doses in order that the desired effects may be achieved

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Treatment is controlled by observing the patient's response by periodic determinations of serum calcium and occasionally by the use of the urinary Sulkowitch test Insufficient treatment is associated with such symptoms as anxiety irritability mental depression and paresthesias of lips and fingers Chvostek's and Trousseau's signs can usually be elicited Overdosage with the activated sterols is quite quickly apparent to the patient because of headache nausea vomiting and an intense dislike or aversion to calcium (Hurxthal and Claiborne) Medication is often discontinued by the patient himself because of the gastro intestinal symptoms Prolonged intoxication from the activated sterols is not likely in patients with tetany because of these reactions In contrast patients with conditions other than tetany who are receiving a high dosage of vitamin D may experience prolonged intoxication without being aware of it It is in such cases that kidney damage and metastatic calcification are most likely to occur

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hormone which in turn causes marked changes in the metabolism of calcium and phosphorus Most of the cases (86 per cent) are caused by a hyperfunctioning parathyroid adenoma and about 14 per cent of cases are the result of hyperplasia or hypertrophy of all four parathyroid glands

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The symptoms are the result of these physiologic changes Hypercalcemia is responsible for muscular weakness and atony constipation loss of appetite loss of weight

and cardiac irregularities The hypercalciuria produces polyuria hematuria renal or ureteral colic and diminished renal function The increased activity of the osteoclasts leads to a generalized decalcification of bones with cyst formation The pathologic changes in the kidneys are of major importance since the ultimate prognosis in any given case is dependent on the extent and severity of the renal damage Renal calculi or calcification occurs in 92 per cent of the cases whereas bone changes are present in only 67 per cent of cases (Keating and Cook) The longer the disease exists the greater is the damage to the kidneys and once the damage is sufficiently marked recovery of renal function will not take place Therefore early diagnosis and proper treatment are of the utmost importance (Lahey)

The only treatment is surgical removal of the offending adenoma or subtotal resection of all four hyperplastic parathyroid glands The diagnosis of primary hyperparathyroidism should of course be firmly established before parathyroid surgery is undertaken The difficulties encountered by the surgeon in locating the adenoma are at times so great that unless the diagnosis is positive the operation may be discontinued short of finding the tumor

Following the operation a state of hypoparathyroidism may develop which demands medical therapy A preoperative serum alkaline phosphatase above 20 Bodansky units and the existence of renal damage are two indicators of the likelihood of postoperative tetany Tetany which occurs as a result of the removal of too much parathyroid tissue is treated in the same manner as tetany which follows goiter surgery Tetany which occurs in the presence of marked skeletal decalcification and increased activity of the osteoblasts (serum phosphatase above 20 Bodansky units) is likely to be severe (Churchill and Cope) The increased demand of the bones for lime salts results in marked lowering of the serum calcium and the serum phosphorus tends to remain low or may even decrease These changes in serum calcium and phosphorus tend to persist until excessive osteoblastic activity ceases and serum phosphatase returns to a normal level at which time parathyroid function reaches normal The treatment of this type of tetany requires a large intake of dietary calcium and in the acute phase frequent intravenous calcium injections may be necessary There are theoretical objections to the use of parathyroid hormone and the activated sterols but nevertheless these may occasionally be used Vitamin D with its greatest action on calcium absorption would seem to be the most desirable

George O Bell

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OVARIAN DISEASES

AMENORRHEA AND HYPOMENORRHEA

Amenorrhea and hypomenorrhea are symptoms rather than disease entities and for this reason treatment should be directed toward the factors producing the menstrual failure But the problem is not simple Although our knowledge of menstrual physiology is far more complete than it was a few years ago nevertheless there are many complex endocrine interrelationships which are either entirely unknown or being known cannot be regulated

In any case of amenorrhea irrespective of

whether primary (the patient being more than 17 years of age and having never menstruated) or secondary (cessation of men struation after it is once established) there are two considerations which are of primary importance and must be investigated before any specific therapy is undertaken First, it must be determined whether there is any gross abnormality of the pelvic structures Vaginal examination is infinitely preferable to rectal examination for this purpose and should be done whenever it is at all feasible In the virginal patient, employing copious amounts of lubricant and using the utmost gentleness, it is generally possible to make a satisfactory one finger vaginal examination and to visualize the cervix Any pelvic abnormalities which are found should be dealt with on their own merits Second, a general evaluation of the patient should be made This will include (1) notation of habitus development of secondary sex char acteristics etc, which may suggest pituitary disease, ovarian agenesia or the like, (2) a detailed physical examination The minimal laboratory studies which should be done are a complete blood count urinalysis basal metabolism and roentgen examination of the chest. The course after this information is assembled will depend in large measure on any abnormalities which are found Devi ations in habitus or development which are considered as endocrine in origin (pituitary, ovarian, or adrenal) are best left for later consideration The immediate effort should be the improvement of the patient's general health Specific advice is given concerning diet, rest the avoidance of excesses and exercise out of doors according to the pa tient s tolerance or inclination Anemia, which is a common finding should be corrected (Except in the anemias specifically requiring liver therapy, it is unusual to find a patient in whom iron by mouth in one form or another is not promptly effective and well tolerated) If the basal metabolism is low thyroid should be given in doses which will elevate the rate to normal or slightly above normal In fact of all therapy avail able for the treatment of amenorrhea thy roid extract is by far the most useful In many cases where the B M R is normal to start with, periodic menstruation is initiated by giving small doses of thyroid to the point

In a significant percentage of cases the measures outlined above will be effective in establishing menstruation If they are not, it must be decided whether or not specific endocrine therapy is warranted, and this decision must by all means be deferred until

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grandmothers can be made to bleed at will by substitution therapy, but this bleeding serves no useful purpose So it is in amenor rhea, the mere production of uterine bleed ing can hardly be considered a therapeutic triumph, unless the therapy causing the bleeding at the same time effects some improvement in the condition which causes the symptom

In primary amenorrhea, it is agreed that no specific attempt should be made to initiate menstruation before the age of 17 because of the frequency with which late puberty may occur up to this time Actually, of course such individuals need no therapy and if left alone will menstruate spontane

trogen therapy is stopped nor is this bleed ing associated with ovulation, since it is of the "estrogen withdrawal type Occasional reports indicate that such cyclic therapy is occasionally followed by ovulation and growth of the hypoplastic uterus, and that true menstruation becomes established Cer tainly such cases are rare I have seen one patient with complete agenesia of the ovaries in whom hysterectomy was necessary to con trol the uterine hemorrhage which resulted from attempts to establish menstruation by the use of estrogens As a rule the treatment of primary amenorrhea should be limited to the routine general measures which were outlined above If one expressly sets out to produce uterine bleeding by substitution therapy, he should do so only with the knowledge that in all probability it will serve no useful purpose except for its dubious psychologic value, and that periodic men

struation will be unlikely unless the therapy is continued indefinitely

In secondary amenorrheas, cyclic therapy with estrogens or progesterone or both may have some occasional use, since periodic menstruation may sometimes continue after the therapy is stopped But it is emphasized that such therapy should be carried on only by one who is thoroughly familiar with the physiology of menstruation, and who is capable of appraising the results he is achieving The important indication for specific therapy is the patient with secondary amenorrhea who complains also of sterility Several regimens have been outlined all of them having entirely unpredictable and doubtful value Stilbestrol (0 5 to 1 0 mg) or its equivalent may be given nightly for 2 weeks, uterine bleeding will follow in about one week, after which the course may be repeated for two or three periods Some have advocated various combinations of progesterone and estrogen though it is doubtful that these are any more effective in producing ovulation than the estrogens alone Gonadotropic hormones are generally agreed to be ineffective Roentgen therapy in small doses to the pituitary and ovaries has recently been advocated However geneticists have shown serious gene mutations in later

should not be lightly undertaken in the human being

DAVID N DANFORTH

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MENORRHAGIA AND METRORRHAGIA

Menorrhagia refers to abnormally profuse or abnormally prolonged menstruation Metrorrhagia refers to bleeding between the periods, and generally is accompanied by menorrhagia Both of these symptoms may have extremely serious implications, and deserve the most meticulous gynecologic study They may result from various pathologic lesions of the reproductive tract, or they may be functional in nature, resulting from known or indeterminate endocrine causes The listing of these possibilities and their therapy is inappropriate in this volume Suffice it to say that, irrespective of the patient's age, it is improper to consider excessive bleeding as functional in nature until curettage has eliminated the possibility of malignancy In younger women this dictum will subject many patients to what may appear to be needless curettage But even if the bleeding is purely functional curettage is frequently followed by marked if often temporary, relief Furthermore, in adolescent patients it is sometimes impossible to make an adequate vaginal examination except under anesthesia, the anesthesia employed for curettage affords opportunity for easy palpation of the adnexa and detection of any pelvic masses which may be related to the bleeding

In addition to curettage and an adequate vaginal examination, there are other determinations which must be made before specific therapy is employed First an evaluation of the patient's general health and physical condition must be made, and any deficiencies corrected If bleeding has been heavy anemia will almost certainly be present and must be treated This responds well to ferrous sulfate—2 gm t i d —and does not require the more expensive combinations of iron with liver and the like, nor is parenteral liver therapy indicated Occasionally, blood dyscrasias may account for menorrhagia, for this reason the bleeding time, platelet count and clot retraction must be tested Also a basal metabolic rate should be taken, since menorrhagia may accompany either hypothyroid or hyperthyroid states, and will usually respond to the correction of this abnormality

If the above investigation has shown no abnormality which might account for the bleeding and if no permanent relief is afforded by curettage, one may then employ sex hormones For this purpose the most generally effective and least expensive preparation is diethylstilbestrol Other estrogens are, of course, equally effective if used in adequate dosage, but before employing any such preparation one must remember that estrogens of all types are specifically contraindicated in the presence of a breast tumor

or family history of cancer of the breast in the presence of cancer of the uterus or in the presence of menorrhagia occurring in the menopausal years The rationale for the use of estrogens in functional bleeding is to produce and maintain endometrial proliferation thus preventing the breakdown of the endometrium which is responsible for the bleeding For this purpose stilbestrol should be employed in high dosage A convenient plan suggested by R R Greene which has been found effective is 50 mg nightly for 4 nights and then 25 mg nightly for 21 nights Uterine bleeding will occur in about one week after the last dose Ordinarily this "menstruation is not excessive and more or less permanent relief may result If there is recurrence of the menorrhagia the plan may be repeated three or four times as may be necessary to control the bleeding This should not be continued indefinitely however and after three or four such trials another complete evaluation of the case must be made which should include curettage as well as the other inquiries mentioned above When stilbestrol is used in this dosage a warning should be given that nausea and vomiting may occur Tolerance is generally developed rather quickly however and the medication should not be discontinued unless there is no improvement after several days trial

Androgens are also effective in the control of functional bleeding although in the author s experience they are less satisfactory than estrogens Divided doses of testosterone propionate may be given over a period of one month the total dosage in any one month not to exceed 250 mg This is reported to give favorable results in something more than 70 per cent of cases Androgens are suggested particularly for those patients requiring prolonged therapy in whom bleeding recurs repeatedly after it has once been controlled For this purpose maintenance doses of 5 to 10 mg of methyl testosterone daily or 10 to 20 mg of testosterone propionate weekly throughout the cycle are claimed to be effective When using androgens one must keep in mind the virilizing possibilities with high dosage or in sensitive individuals All of these effects are considered reversible when the drug is stopped except for voice changes which ordinarily are permanent once they have been produced

Finally pitressin tannate in oil has recently been found useful in the management of functional bleeding A single intramuscular injection of 2 cc or 10 pressor units is given The therapy is advocated particularly for the control of the initial episode and is reported to be effective in 1 to 2 days and to last for 2 to 4 days No formal confirmation of the original report is available at this

antidiuretic hormones are observed

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DYSMENORRHEA

The term dysmenorrhea may have either of two entirely distinct connotations First it may refer to one of the symptoms of certain organic lesions of the reproductive tract secondly it may refer to the ill defined condition commonly regarded as an entity of so called idiopathic dysmenorrhea in which no organic abnormality is demonstrable This chapter is concerned with the latter and presupposes that organic dysmenorrhea is ruled out by a full history and by accurate bimanual examination The pattern of idiopathic dysmenorrhea is extremely variable It may start with the first menstruation more

more or less constant in one individual may be either days or hours before the onset of the flow coincident with the onset of the flow or after the flow has started the pain may last for hours or days may be mild or

be coincident vomiting diarrhea, or both Although innumerable articles purport to explain this syndrome, there is as yet no adequate demonstration of a mechanism common to all cases Hence, therapy remains empirical The observation that the pain threshold is low in a high percentage of patients with dysmenorrhea is of no interest in management except in the occasional case where psychoneurotic factors or conditions of maladjustment in the home can be shown to operate Such factors should of course be uncovered and dealt with so far as possible But irrespective of whether the pain threshold is high or low these patients may not be summarily dismissed as emotionally unstable They require help, and are entitled to the physician s best effort

Since therapy is empirical it is necessarily somewhat unsatisfactory Some cases respond promptly to the simplest of indirect measures, while others are intractable to the most specific efforts

General Measures In all cases inquiry should be made concerning the patient s habits and also of the reaction of the parents or husband to this periodic illness This may give valuable information concerning important contributory factors In addition

hygienic measures including a balanced diet adequate rest, and healthful exercise out of doors, are important and must not be overlooked

Exercise It is well known that in many cases of intractable dysmenorrhea, stretching exercises of various types may give dramatic relief Those recently outlined by Haman have been used by the writer repeatedly and with much satisfaction They are the following

Position I Stand at right angles to the wall at such distance as will enable you to rest the left elbow comfortably on a level with shoulder Tilt the pelvis forward, and, while in this position, touch the wall with the hip, keeping knees straight Take care not to twist the body or allow the elbow to slide on the wall

Position II Same as above, using the right elbow

Position III Face the wall, and rest both elbows at the level of the shoulder Tilt the pelvis forward until the pelvis

peat three times daily The extreme exercise of this type, ballet dancing may appear to be a heroic measure, nevertheless when simple exercises fail, this may be effective, and should be tried

Medications Any of the analgesic drugs may be employed, some more effectively than others A combination which has been found useful is a capsule containing

Ephedrine	0 02	gm
Atropine	0 0002	gm
Aspirin	0 3	gm

If this is not effective, because of the severity of the dysmenorrhea, codeine (0 015 or 0 03 gm) may be substituted for the aspirin It is considered important that the patient have positive relief to fall back on, and codeine should not be denied merely because it is an opiate

The use of hormones and surgical procedures is not included in the recommendations made here Some have advocated large doses of estrogens for the purpose of inhibiting ovulation so that the next "menstrual" period will consist only of painless withdrawal bleeding This is purported to have a salutary psychic effect, although to the writer this seems of dubious value Progestational and androgenic hormones, except as they may inhibit ovulation are of little use Surgical procedures may be employed only as a last resort, after all other possibilities have been exhausted Dilatation of the cervix and insertion of a stem pessary, formerly so fashionable, has fallen into disrepute for the reason that its chief effectiveness is considered to result from the heavy psychologic impact, the appropriateness of which may be questioned Presacral neurectomy gives a high incidence of relief, but this is a major transperitoneal operation in which even in skilled hands complete removal of the presacral nerve is difficult It is noteworthy that many prominent gynecologists of wide experience have never found it necessary to employ this procedure for the relief of dysmenorrhea

Finally, one should remember that it is unusual for idiopathic dysmenorrhea to con-

tinue after a term birth, and that irrespective of pregnancy there is often significant spontaneous improvement after the age of 25 or 27

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THE MENOPAUSE

Of all the conditions which the physician is called on to treat, the symptoms associated with the menopause appear to be among the most poorly managed The important reason for this is the easy availability of preparations which, although they will achieve temporary relief, may have a deleterious effect on the fundamental condition from which the symptoms arise

At the outset, it should be emphasized that the "menopause should not be employed to cover bizarre or apparently inexplicable symptoms which may have their onset in the menopausal years The only symptoms which are characteristically typical of the menopause are the cessation of menstruation and vasomotor disturbances Other symptoms, even though they may be coincident with those mentioned, demand the same respect which they would receive if they occurred at any other age Many nervous gastro intestinal and cardiorespiratory disturbances have their onset in both men and women of this age group To be sure, many such complaints are wholly functional and result from the apprehension and emotional tension which sometimes attend the menopause But when they exist without at least one of the two fundamental symptoms of the menopause, or when they are not promptly ameliorated by the menopausal therapy outlined below they must then be considered as unrelated to the menopause per se and investigated as such One often hears of a so called "therapeutic test with estrogens,' in which these substances are given as therapy, for example, of a mild anxiety state or melancholia In such a case no permanent good may be expected from this therapy, rather, the condition should be recognized as psychiatric, and appropriate measures taken Also, it should be emphasized that excessive bleeding is decidedly not a symptom of the menopause Too frequently menorrhagia having its onset along with vasomotor symptoms or in the menopausal years, is disregarded Excessive bleeding at any age demands specific investigation, namely, curettage and microscopic study of the tissue obtained

Once the diagnosis of 'menopausal syndrome" is made, therapy should be directed not toward the achievement of complete relief, but rather toward reducing troublesome symptoms to the point of easy tolerance With this as a goal it is apparent that therapy must be individualized, and that what is proper for one may be highly improper for another Measures ordinarily undertaken include the following

General Measures Many women of this age group benefit greatly from measures designed to improve their general health Particular inquiry and investigation should be made concerning such possibilities as low grade anemia or hypothyroidism and if found they should be corrected Specific advice should be given concerning a balanced diet rest diversion from routine household tasks and responsibilities and mild exercise out of doors

Reassurance This forms an extremely important part of any regimen, but is perhaps of greatest importance in those who are about to enter the menopause or are experiencing the preliminary symptoms Well-meaning friends and relatives are often most articulate with respect to the description of symptoms which they have experienced and the shots" which were necessary for their control The impact of such reports is heavy, with the result that many women approach the menopause with dread and full expectancy that it will mark the end of their mental vigor and equilibrium It is of the greatest importance that women be made aware of the facts, first, that by far the great majority of women pass the menopause without incident and second, that a large number of those who encounter difficulty do so for reasons ascribable directly to improper therapy Also, many women approach the menopause with fears of insanity, or apprehension that sexual desire and satisfaction will be impaired These women must be reassured that the occasional onset of insanity

has nothing whatever to do with the menopause per se any more than does its similar incidence in men of the same age group, *also, it is unusual to find sexual* gratification or desire impaired in women who have already established a satisfactory pattern of sexual activity

Sedation In a case in which vasomotor symptoms are less than extreme, and when nervousness and irritability are present mild sedatives are often of great benefit In fact, most menopausal patients can be controlled with such drugs alone Phenobarbital in doses of 0 015 to 0 03 gm three times daily, may be given When sedatives are employed in this manner, the primary objective is to *avoid the use of estrogens* However, it is necessary to explain to the patient that she may have some discomfort, and that if it is more than she can easily tolerate other drugs will be prescribed

Estrogens There are three major principles which govern the use of estrogens in the management of the menopause These are the following

(1) Estrogens are orally active, and need not be given parenterally Controlled studies have demonstrated beyond question that it is only in the exceptional case that oral prep*arations are not effective and well tolerated* by the patient

(2) The indiscriminate use of estrogens in an effort to eliminate all menopausal symptoms can greatly prolong the menopause

(3) Estrogens are specifically contraindicated in the presence of a breast tumor or family history of cancer of the breast in the presence of cancer of the uterus, or in the presence of menorrhagia

Employing these tenets one proceeds to the estrogen therapy of menopausal symptoms in the following manner First, a careful examination and history must eliminate the conditions mentioned under (3) Second, the patient must be advised that the objective of this therapy is to reduce the symptoms only to the point where they can be readily tolerated It is necessary to explain here that *although it is quite possible* to relieve the symptoms entirely, by so doing the duration of the menopause may be in*creased* Furthermore, it should be pointed out that the period of time the patient is to receive estrogens should be limited and should preferably not exceed 6 months

Many excellent oral estrogens are available The most commonly employed, as well as the least expensive, is diethylstilbestrol For the control of ordinary menopausal *symptoms, this should be prescribed in doses* of 0 5 mg or less at bedtime daily for 2 to 6 weeks, followed by a smaller dose, as 0.2 mg, nightly or every other night for the next 4 to 6 weeks In occasional cases larger doses will be required, but irrespective of the severity of the symptoms, the smaller doses should be tried first At the end of this period, the patient should be instructed to decrease the frequency, with the view to eliminating the medication *all* together within 6 months At all times the smallest effective dose should be used, and the effort should be made to use this as infrequently as may be possible for adequate control of symptoms

Occasionally stilbestrol is accompanied by undesirable side effects, such as nausea and vomiting This is most frequent when doses of more than 0 5 mg are required for control of symptoms However, tolerance is generally developed rather quickly, so one need not discontinue the medication immediately *for this reason* In those whose reaction is marked or where no tolerance develops one may employ other oral estrogens, as premarin, hexestrol, ethinyl estradiol or the like or, exceptionally, hypodermic therapy such as di ovocylin 2 5 to 5 mg intramuscularly Irrespective of what estrogen is used one should be governed by the principles which have been outlined, and should aim specifically at the avoidance of addiction, whether the medication be in the form of tablets, or whether it be "shots"

Androgens Androgens are effective in relieving menopausal symptoms in the same measure as are estrogens and should be employed in like manner and with similar objective As noted by Gusberg androgens are specifically urged *for necessary* endocrine therapy of the menopause in the following situations

(1) Patients who have a family history of cancer of the breast, who have a breast tumor, or who have been treated for cancer of the reproductive tract or breast

(2) Patients who have been treated for abnormal uterine bleeding during the climacteric
(3) Patients who develop troublesome uterine bleeding while under treatment with estrogens
(4) Patients requiring endocrine treatment for vasomotor symptoms before complete cessation of the menses
(5) Patients addicted to stilbestrol through long usage

Methyl testosterone may be given by mouth in doses of 20 mg daily for 4 weeks and then 10 mg daily for 2 weeks Such doses are ordinarily effective and are generally less than the amounts needed to produce masculinization

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TESTICULAR DISEASE

STERILITY IN THE MALE

Treatment of male sterility is begun when it has been established that the wife is apparently normal and that the fault of the childless marriage lies with the husband Therefore it is essential that the wife have a complete physical examination including a tubal patency test before proceeding with treatment of the husband It is now recognized that approximately 50 per cent of childless marriages are the result of male sterility

In order to deal properly with male sterility it becomes necessary to point out the causative factors and their management

Physiologic Sterility This condition is found in boys in the prepuberal age group and in old men whose sexual functions have been exhausted It is hardly necessary to say that no treatment is indicated

Local Pathologic Conditions This deals with the absence of testicles either congenital or acquired through injury or surgical castration There is no treatment for this con [illegible]

(2) Orchiopexy
(3) Hormonal therapy with chorionic gonadotropic hormone (anterior pituitary like hormone) One commercial preparation that may be used is korotrin extracted from the urine of pregnant women and marketed by Winthrop Stearns Company The suggested dosage is 100 international units given one week later and 200 international units given three times a week for a 6 to 8 week period

Some cases will show descent in 3 weeks and others will require longer treatment If there are no results in 8 weeks the hormone therapy will probably not be successful and its administration should then be discontinued

Another hormone preparation is antuitrin S made by Parke Davis and Company It is made by extracting the hormone from the urine of pregnant mares The dosage of antuitrin S as suggested is 500 international units given intramuscularly three times a week If there is no evidence of response to the treatment after 2 weeks a rest period of 1 month is allowed after which 500 international units are administered again three times a week for 6 to 8 weeks

In any therapeutic regimen using gonadotropic hormones excessive development of the external genitalia and of the prostate must be prevented If such growth appears excessive the treatment should be discontinued

Atrophy and destruction of testicular tissue due to mumps suppurative orchitis ischemia of the testes or roentgen or radium emanations are not amenable to treatment

Testicular tumors are usually malignant and if enough testicular tissue has been replaced by tumor tissue to cause sterility there is no treatment

Chronic orchitis is usually due to tuberculosis or syphilis and these diseases are given priority in the therapeutic plan In any case a chronically diseased testicle probably never will produce adequate healthy spermatozoa

Prostatovesiculitis may be a factor in sterility It would seem advisable to clear the seminal fluid of pus which quite possibly would have a *deleterious effect on the spermatozoa* The following program is suggested

(1) Biweekly prostatic massage and stripping of the seminal vesicles As the fluid is expressed a drop is examined under the high dry lens of the microscope and the number of pus cells per high power field is counted and recorded This is done at the time of each massage In this way the progress can be charted by watching the number of pus cells decrease Some patients will respond in one or two treatments and others will be more resistant as evidenced by the persistence of high pus cell count

(2) Penicillin S R (Parke Davis and Company) is given in single daily intramuscular injections of 300 000 units every other day for a week Depo penicillin (Upjohn Company) may be given in the same dosage of 300 000 units at each injection

(3) Sulfadiazine 0 5 gm given orally with *sodium bicarbonate* 0 6 gm three times a day for a 7 day period

(4) Fluid intake of 8 to 10 glasses of fluid per day is advisable

(5) Bowel evacuation if indicated by mild *catharsis such as cascara sagrada* aromatic fluid extract 1 dr or a 5 grain tablet of cascara given at bed time

(6) Complete abstinence from alcoholic beverages and spicy *foods*

Obstructions and deformities of the genital tract are treated by surgery where possible In obstruction of the epididymis and adjacent scrotal portion of the vas deferens epididymovasostomy may be *of some help* Obstructions higher than this point cannot usually be corrected by surgery Hypospadias and urethral strictures are usually amenable to corrective plastic surgery

General Pathologic Conditions ENDOCRINOPATHIES deal with the following conditions

(1) *Hypothyroidism* The severity of this *disease is determined* by the history and physical findings including a basal metabolism determination Thyroid extract will correct this condition

(2) *Hypogonadism* There is little that can be done for this symptom complex The benefits obtained from the use of testosterone are questionable because administration of this hormone tends to depress spermatogenesis

General debilitation and chronic alcoholism are often contributing factors to sterility and they are treated along the lines of prescribing diets high in protein calories and vitamin content

Vitamin E deficiency is known to be a factor in the production of abortion in animals but its role in sterility is questionable

Impotence is a factor sometimes met with which causes a pseudosterility in that there may be adequate healthy spermatozoa but the patient is unable to make delivery The treatment of this condition is discussed elsewhere

The treatment of sterility begins with the first visit of the patient to the doctor s office *At this time a careful history is taken* not only of the duration of sterility history of mumps etc but of a general nature to bring out past diseases and operations which might shed some light on the problem for example a *patient may be quite fertile* but unable to transmit the spermatozoa to the cervical region because of psychologic impotence yet this patient will in all probability be most reluctant to discuss his inabilities until the *physician wins his complete confidence* by tactful questioning in an understanding manner

At the time of the first visit to the office a physical examination including blood pressure *temperature pulse rate* urinalysis and rectal digital examination of the prostate is done Microscopic examination of the prostatic fluid and palpation and inspection of the external genitalia are also recorded Next *the patient is instructed to* bring in a speci

men of semen for examination and spermatozoa count The specimen is best collected by ejaculating into a wide mouthed bottle at the conclusion of intercourse The patient should be advised to abstain from coitus for a week before bringing in a semen specimen Condom specimens are unreliable because the rubber and certain spermicidal powders applied to the sheaths by the manufacturer will give an inaccurate count of nonmotile spermatozoa The specimen should be brought in to the doctor or the laboratory as soon as possible and not later than 4 hours after intercourse in order to determine accurately the degree of motility of the spermatozoa

Technic of Counting Spermatozoa

(1) Diluting fluid is made up with sodium bicarbonate 5 00 gm Formalin 1 00 cc Distilled water 100 00 cc
(2) After mixing the specimen well draw semen up in a leukocyte counting pipette to the 0 5 mark
(3) Dilute with the diluting fluid up to the 11 mark
(4) Allow to stand at least 10 minutes without shaking to permit the sodium bicarbonate to counteract the mucus
(5) Shake the pipette for 3 minutes
(6) Plate out the mixture on a counting chamber and count as for a leukocyte count under the high power lens
(7) Calculate as for a leukocyte count and add two zeros to determine the number of spermatozoa per cubic centimeter

Technic of Staining Semen

(1) Air dry a thick smear on a glass slide
(2) Stain for 30 to 60 seconds with carbol fuchsin
(3) Wash gently with water
(4) Counterstain with methylene blue
(5) Wash and air dry
(6) Examine under the oil immersion lens

Semen Requirements for Fertility

(1) Spermatozoa count of from 60 000 000 to 100 000 000 per cubic centimeter
(2) About 85 per cent of the spermatozoa must be actively motile
(3) About 85 per cent of the spermatozoa must be morphologically normal
(4) The volume of the ejaculate ranges from 2 to 5 cc. the average being 3 cc

Ambulatory treatment of the patient showing a low sperm count and/or nonmotile or morphologically poor spermatozoa

(1) Thyroid administration of ½ to 1 grain a day with careful observation for signs of toxicity Thyroid is given empirically in the absence of evidence of hypothyroidism because an increased metabolic rate has been shown to raise the sperm count and to increase sperm motility
(2) Hormone therapy with gonadotropic factors is carried out in the same dosage as described under cryptorchism
(3) General measures such as total abstinence from alcohol adequate diet mild to moderate exercise especially for the sedentary office worker and plenty of rest including at least 8 hours of sleep each night

General Discussion This discussion has been limited to the problem of treating sterility in the male Several causes have been presented but it must be emphasized that most cases will be due to some unknown or undemonstrable etiology Therefore the suggested ambulatory treatment will apply in most instances Reference has been made to certain commercial gonadotropic hormone preparations this is not necessarily an endorsement of these products but a famili

achieved in the treatment of male sterility will be most gratifying in some cases and discouraging in others but at the present time there seems to be no other way of attacking the problem

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IMPOTENCE

Impotence is a condition in which there are varying degrees of inability on the part of the male to have normal sexual intercourse Impotence is not synonymous with sterility although clinically the two conditions must often be regarded and treated to-

gether A fertile man may be impotent and an impotent man may be fertile, although he is clinically sterile, or rather he has a pseudosterility because of his inability to implant the spermatozoa where they can subsequently fertilize the ovum The degrees of impotence run from premature ejaculation to complete loss of erection

A complete history of the difficulty, particularly *of sexual habits, palpation of the* prostate with microscopic examination of the prostatic fluid for pus cells examination of the external genitalia, and a urinalysis should classify the disorder as to its underlying etiology, i e, organic or functional Urethroscopy adds much to the diagnosis and treatment by ruling in or out lesions of the posterior urethra such as inflammation congestion, or such evidence of chronic infection as granulations and polyps about the region of the verumontanum

Impotence may be classified as being of an organic or of a functional nature Treatment of organic causes of impotence depends for *its success on the removal or correction* of the cause, if possible

Organic Causes LESIONS OF GENITALIA

(1) Penile inflammations are treated specifically as *other infections* with chemotherapy and surgical principles

(2) Curvature of the penis is usually not amenable to treatment because of the nature of the underlying lesion The curvature is due to unequal engorgement during erection of the corpora *cavernosa resulting from* fibrosis and scar formation, which prevents the blood from distending a portion of the corpus cavernosum Any surgical attempt at removal of the scar tissue is likely to result in more scar formation with unsatisfactory or even worse results

(3) Urethral strictures are treated by dilatations with sounds or by internal urethrotomy, or external urethrotomy, depending on the extent and location of the stricture

(4) Inflammatory lesions about the verumontanum *and granulations* and polyps of the posterior urethra respond well to local instillations of silver nitrate, 1 per cent in 3 to 5 cc amounts through a no 14 urethral soft rubber catheter This may be done once a week for a 4 to 6 week period, at the same time increasing gradually the strength of the silver nitrate up to 2 per cent If this plan of treatment *does not help, it is* advisable to cauterize the urethral polyps and granulations with the high frequency cautery current transurethrally

LESIONS OF THE NERVOUS SYSTEM

(1) Tabes dorsalis
(2) Tumors and injuries of the spinal cord
(3) Cerebral lesions

These lesions are not amenable to the treatment of impotence, also these lesions are serious and of primary importance the impotence is relatively unimportant

ENDOCRINOPATHIES *Frolich's syndrome* may respond quite satisfactorily to treatment *with the gonadotropic hormones* The same dosage is used in this syndrome as discussed under cryptorchism in the section on Treatment of Sterility in the Male

Absence of testicular tissue may be treated by the administration of testosterone propionate in oil intramuscularly, 10 to 25 mg two or three times a week Methyl testosterone *is given orally in doses of* 30 to 60 mg daily Because this is a form of replacement therapy, the benefits are derived only as long as the administration of the hormone is continued

Hypothyroidism is best treated by the administration of adequate doses of thyroid substance

PHYSIOLOGIC IMPOTENCE Functional impotence comprises about 95 per cent of the cases that present themselves to the physician *However, in order to treat* the cause of impotence such cause must be searched for, be it organic or functional There is no indication for treatment of physiologic impotence due to old age *There have been* attempts, both medical and surgical, at rejuvenation but these for the most part have met with failure Sometimes an older man will seek renewed sexual powers and occasionally he will regain them through one device or another, but the alleged good results are temporary and short lived

Functional impotence may be so complex as to require the services of a psychiatrist However, there are some things that the

physician can do which will offer assistance toward improving or curing the condition Among these are

(1) General measures such as improving the general state of health by vitamins, proper diet, adequate exercise, removal of worries and anxieties, and insistence on 8 hours of sleep at night

(2) Psychotherapy in the form of impressing on the patient that his difficulty is mental and that he will be cured An interview with the patient's wife is often essential in order to bring about her understanding of the problem and thus secure her co operation Any difficulty in this direction may be overcome by pointing out to her that she, too, benefits from the treatment The patient with premature or rapid ejaculations is advised to try to approach the act of intercourse as calmly as possible and to lengthen the time by diverting his thoughts from the business at hand

(3) Sedation in the form of elixir or triple bromides, 1 dr twice a day after meals in water, is helpful for the patient troubled with premature ejaculation

(4) Hormonal therapy with the gonadotropins probably has little to offer, however, it might be wise to use it empirically as in certain cases of sterility There are reports of success from hormonal therapy Whether it is the hormone or the psychologic effect of the needle and syringe on the patient makes little difference The object is to treat the impotence

JAMES I FARRELL

CHAPTER V

DEFICIENCY DISEASES

VITAMIN DEFICIENCIES

GENERAL CONSIDERATIONS

Vitamins are constituents of enzyme systems and are essential for the metabolism, development, and reproduction of bacteria and animals Most vitamins are synthesized by the animal organism inadequately, if at all, and the vitamins themselves, or their precursors, must be present in the diet In their absence, clinical signs of deficiencies and even death may occur

Although many vitamins exist and have been described only seven deficiency diseases which have been observed in man and which are of dietary origin are discussed here Some of the vitamins omitted from the discussion may be essential to man under special experimental conditions Some, while not synthesized by the body tissues, can be formed in sufficient amounts by intestinal bacteria from precursors and related substances to make up for inadequacies in the diet Thus, the human dietary requirements may vary widely, depending upon physiologic or pathologic stress and other constituents of the diet, as well as caloric intake

Prevention of Vitamin Deficiencies

single foodstuff which in itself supplies an adequate diverse vitamin intake, the diet must be well chosen and should include 1 pt (0 5 liter) of milk, whole or skimmed, or one serving of cheese one or two eggs, one adequate serving of fish, meat, or poultry, two leafy green vegetables and one yellow vegetable (these may be cooked or raw), one whole grain cereal with additional milk or cream, two slices of enriched bread with 2 teaspoons of butter or vitamin A fortified margarine, freshly prepared citrus fruit or fruit juice, and another fresh or cooked fruit

Additional vitamins in concentrated form may be added when the diet is unsatisfactory or is restricted because of obesity, diabetes, or food allergy, when the requirements are increased by infection, surgery, or metabolic disturbances, or to supplement infant feeding where the rapid rate of growth increases the need for vitamins

Vitamin Preparations The number of mixed vitamin preparations now available commercially and the promotional claims made for each have created considerable confusion Many preparations include minerals and vitamins for which actual human need has not been proved

The accepted synthetic vitamins may be used effectively and interchangeably with the natural ones They are usually much cheaper than the purified vitamins derived from natural sources, but have the disadvantage that they contain none of the trace substances of possible nutritional significance found in the latter

It is important that the physician have available an authoritative source giving the recognized action, use, and dosage of vitamins, and that he examine the labels of vitamin preparations, comparing them with other products and with the statements and advertising claims offered The amounts of vitamins in the mixtures used should be related to the dietary requirement Vitamin mixtures should not supplant preventive and therapeutic dietary measures, but merely supplement them

Vitamin Requirements In most instances the daily allowances recommended by the National Research Council (1934) are undoubtedly greater than the minimal requirements for health There is no clinical

evidence that the body stores must be saturated by vitamins for the body to function normally

The possibility that deficiency diseases may develop in chronically ill patients must be anticipated by the physician so that effective prophylaxis or therapy may be instituted This is also true of other conditions where the normal requirements may be altered as for example during pregnancy The increased frequency of deficiencies occurring during pregnancy even on a minimally adequate diet suggests that an increased vitamin intake may be necessary at such times

Sulfonamides are known to affect vitamin synthesis The effects of the newer antibiotics such as penicillin streptomycin aureomycin and chloromycetin on the synthesis of vitamins by intestinal bacteria are still unknown

While little is known of the vitamin requirements of old people there is little evidence that the need for vitamins increases

and to poor living conditions and habits Old people may be confined to their rooms receive little ultraviolet radiation have poor appetites and be unable to prepare or eat meals of adequate vitamin content Improperly fitting dentures or lack of teeth institutes a vicious cycle which may result in gastrointestinal disturbances and still further restriction of the diet Such manifestations of dietary deficiencies should yield to specific treatment properly administered Senile

order to treat a patient successfully it is necessary to combine specific vitamin therapy with that of any coexisting disease

foodstuffs are best taken by mouth Parenteral administration is justified for those patients who are unable to take food by mouth for those having defects in intestinal absorption and for those with such an acute deficiency that any delay in replacement is inadvisable

Laboratory procedures which measure vitamin levels in the blood or the amounts excreted in the urine before and after a test dose of vitamins have been employed as diagnostic aids For the most part they are technically difficult to perform expensive and subject to misinterpretation As a result it is the practice of many physicians to give vitamins as a therapeutic test when the patient s dietary history and symptoms suggest an underlying deficiency state Mild subjective improvement in such a patient is difficult to evaluate In persons having actual deficiencies the use of a potent purified vitamin compound is usually followed by a satisfactory response in 1 to 3 weeks

A trial of brewers yeast or liver extracts or parenteral administration of vitamins or liver may be necessary if oral treatment is ineffective No benefit can be anticipated unless a need for therapy exists

There is no irrefutable evidence that healing and regeneration may be hastened or improved by the administration of large amounts of vitamins unless a deficiency exists There is no rational basis for "overdose" therapy Although increased excretion of vitamin substances does occur during certain pathologic conditions an adequate diet is in most instances all that is necessary to compensate for this loss

Both clinical and laboratory studies have shown that deficiency diseases are seldom due to the inadequate ingestion of only one vitamin Infantile scurvy and rickets which may be seen singly and uncomplicated are exceptions In general the necessity for balanced multiple vitamin therapy is accepted and indications for the administration of single vitamin substances are rare

The interaction of vitamins with each other and the fact that the requirements of one may be affected by the intake of the others have been definitely proved Excessive dosage of a single vitamin even if it is nontoxic itself may precipitate signs of a deficiency of another vitamin For example patients with beriberi who are treated with thiamine alone may then develop evidence of a niacin deficiency

Summary The unrestricted purchase of vitamins over the counter without a doctor's recommendation or prescription should be discouraged. The most dependable source of vitamins are the natural foods of an adequate diet, and in most instances families of low income would do better to use the dietary portion of the budget to purchase a good variety of wholesome food rather than purified vitamin preparations. The great amount of publicity given to vitamins has created the erroneous impression that the only way to maintain health is by taking accessory vitamins. It behooves the doctor to consider well whether accessory vitamins are needed and when they are, to select carefully the preparation which is best suited to the patient's needs.

DAVID CAYER

VITAMIN A DEFICIENCY

Xerophthalmia and Keratomalacia Vitamin A activity is found in a number of different natural and synthetic chemical compounds. Those found in plants (provitamins A) are converted by the animal liver into substances having vitamin A activity. At least nine naturally occurring provitamins A and two vitamins A are known.

Absorption and Storage of Vitamin A The absorption of vitamin A and carotenes (provitamins A) is favored by the presence of fat in the intestines. For absorption of carotene, bile salts are also necessary. The conversion of carotene to vitamin A in the liver is slow and probably not more than 50 per cent complete. In the presence of liver damage even less conversion occurs. Disturbances of fat metabolism which may be anticipated in such conditions as the sprue syndrome, cystic fibrosis of the pancreas, bile duct obstruction or disturbances of [illegible] result in defective [illegible] Chil[illegible] who are deficient in pancreatic enzymes can absorb the vitamin A alcohol but require pancreatin for the absorption of the ester (the predominant form).

Interference with absorption by inert hydrocarbon oils (mineral oil) is exaggerated as a nutrition problem.

Vitamin A is stored in the liver in large quantities. In persons eating a good diet the vitamin A stores of the liver increase over the years of adult life. Normal individuals with adequate body reserves of vitamin A can go as long as 6 months on a diet deficient in vitamin A before the plasma levels of vitamin A are depleted and often as long as a year before clinical signs of a deficiency develop. In view of the marked ability of the body to store this vitamin, indications for parenteral administration are rare.

Requirements of Vitamin A Recent studies on varying dietary intakes of vitamin A indicate that less than 5000 units daily are required. In adults on daily intakes of 2000 units of vitamin A the blood serum contains 20 to 35 units per 100 cc (Normal 75+ I.U.), and symptoms of vitamin A deficiency improve. On an intake of 2500 units of vitamin A, symptoms of a specific deficiency are relieved and the vitamin A content of the blood reaches normal levels. It would seem therefore that in most instances a daily intake of 2500 units of vitamin A is probably in excess of the amount required to maintain normal nutrition. The daily requirement for women during pregnancy and lactation is probably higher, but still below the 6000 to 8000 units recommended by the National Research Council. Infants up to one year of age can probably be maintained on approximately 25 units of vitamin A per kilogram of body weight daily. Present feeding practices make it improbable that they will suffer from an inadequate intake of vitamin A.

In 1946 the A.M.A. Council on Pharmacy and Chemistry refused to accept vitamin A preparations containing more than 25 000 units per dose. The Council was not concerned with the toxic effect of vitamin A but felt that there was no justification for the routine administration of doses in excess of 25 000 units per day.

Therapy BY DIET The treatment of dis[illegible] deficient intake of vitamin [illegible] precursors. The vitamins A occur in nature only in animal tissue. Vitamin A in the diet is thus derived either preformed from ingested animal tissues or from vegetables as the provitamin. Many carotenoid pigments synthesized by plants are converted by the liver into vitamin A. The foods which con

tribute vitamin A precursors to the diet are yellow and leafy green vegetables such as turnip greens spinach carrots squash and sweet potatoes Peaches and tomatoes also contain provitamins A Animal livers are rich sources of preformed vitamin A as are kid neys milk and milk products and eggs Fortified oleomargarine also contains preformed vitamin A in amounts up to 9000 units per pound

By Oral and Parenteral Administration of Vitamin A There is little reason why any one on a normal varied diet should become deficient in vitamin A If for any reason the diet is restricted daily supplements of vitamin A up to 5000 international units may be pre scribed This may be given in any of the preparations containing vitamin A alone or in liver oil concentrates containing vitamin A with other fat soluble vitamins Where a vitamin A deficiency exists vitamin A is preferable to the carotenes for therapy in the treatment of the condition

A daily supplement of 5000 U S P units has been reported to be as effective as 150 000 units given daily The healing of skin lesions is slow often requiring months Excessive doses do not result in more rapid healing In the treatment of various ocular symptoms resulting from a deficiency of vita min A children who received 25 000 to 30 000 U S P units of vitamin A daily did not recover more rapidly than those who received smaller doses The absorption of vitamin A and carotene from large single doses is limited Multiple small doses given two to three times a day are therefore more effective therapeutically

Cod and other fish liver oils are excellent sources of vitamin A Commercial prepara tions of vitamin A are chiefly concentrates of fish oil distillates It is far better to give vitamin A orally than intramuscularly Par enteral injection of the fat soluble vitamins poses a special problem unless a water soluble preparation of the vitamins is avail able Such preparations of vitamin A can be obtained and are suitable for intramuscular injection When given intramuscularly in oil vitamin A is slowly absorbed It does not provide an immediate available source for body needs Utilization of the carotenes after parenteral injection is even less efficient than that of vitamin A

Other Uses of Vitamin A Vitamin A therapy has been reported to be beneficial in two rare follicular dermatoses (keratosis fol licularis and pityriasis rubra pilaris) In all probability these disorders do not represent

use of vitamin A in the local treatment of burns and wounds Vitamin A is ineffective

or no value in the prophylaxis or treatment of acute infections or in enhancing immu nologic reactions The lowered resistance to infection which is associated with severe vitamin A deficiency is probably related to secondary morphologic changes in the pro tecting epithelial barrier

Toxicity of Vitamin A Large doses of vitamin A are well tolerated although in toxication in adults has been reported after as little as 40 000 international units daily Severe hypervitaminosis A has also been re ported in children receiving as much as 240 000 units daily over a period of several years The condition is characterized by headache drowsiness dizziness dermatitis hepatomegaly splenomegaly hypoplastic anemia leukopenia increased serum lipid and vitamin A levels and clubbing of the fingers Usually however only normal vita min A levels are maintained even when excessive amounts of vitamin A are ingested

Excessive intake of carotene has been re ported to result in similar changes As a rule however a harmless yellow discolora tion of the skin which disappears rapidly when carotene is withdrawn is the only manifestation

Preparations of Vitamin A Vitamin A is usually prescribed as a fish oil preparation or a solution of carotene the vitamin pre cursor Cod liver oil U S P contains a mini mum of 850 units of vitamin A per gram The cod liver oil preparations included in the New and Nonofficial Remedies vary in potency from 850 to 2100 units per gram *The dose must be determined by the strength of the particular preparation used* The ad vantage of cod liver oil as a source of vitamin A is its low cost The disadvantages are the taste and volume which must be taken It

may, however, be flavored by the addition of not more than 1 per cent of an official flavoring substance

The disadvantage of taste can be overcome by the use of cod liver oil concentrates in capsules Those included in the New and Nonofficial Remedies contain a minimum of 14 000 units of vitamin A per gram The vitamin D content is increased proportionately Natural vitamin A in oil, U S P, contains between 50 000 and 65 000 units of vitamin A per gram (1 cc weighs approximately 0 9 gm) Percomorph liver oil contains 60 000 units of vitamin A per gram It also contains large amounts of vitamin D

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VITAMIN B THIAMINE DEFICIENCY

Beriberi Thiamine is essential in the intermediary metabolism of carbohydrates It acts as a *co-enzyme and by oxidation prevents* the accumulation of pyruvic acid in the blood When deficiencies of thiamine exist severe physiologic cellular disturbances usually most marked in the neurones of the central nervous system occur Severe and prolonged thiamine deficiency leads to the clinical signs and symptoms of beriberi, in the wet form the permeability of membranes is altered

ABSORPTION AND STORAGE OF THIAMINE Thiamine is readily and almost totally absorbed from the normal gastro intestinal tract and after intramuscular injection Excess amounts are excreted after a few hours chiefly in the urine as the free unphosphorylated vitamin Increased alkalinization of the gastro intestinal tract increases the destruction of thiamine Certain adsorbents such as *magnesium trisilicate and kaolin also reduce* its absorption

The vitamin is not stored in the body to a great extent The total thiamine storage of [illegible] Thia[illegible] de[illegible] [illegible]rmal subjects on a thiamine free diet develop signs of a deficiency in 20 to 40 days

REQUIREMENTS OF THIAMINE. Various estimates of the *minimal requirements* of thiamine for a moderately active man with a caloric intake of 3000 calories range from 0.2 mg up to 0.5 mg per 1000 calories It is felt by most investigators that 0 24 to 0 45 mg of thiamine per 1000 calories will protect *against a deficiency* of this factor Others, however, give 0 45 mg as the lower limit of the minimal range for 1000 calories Deficiencies have been produced on diets containing 0.20 mg per 1000 calories A diet high in carbohydrate increases the requirement for thiamine, whereas a diet high in fat decreases it

The studies of Keys and Henschel indicate that healthy young men expending 3740 to 4200 calories per day require no more than 1 7 mg of thiamine No additional benefit is derived from the ingestion of 1 mg for each 1000 calories of food

It has been demonstrated that thiamine can be synthesized by bacteria in the bowel of human subjects and utilized to furnish part of the body's requirement This is not a major source of supply, however

It is probably safest to believe that thiamine requirements are increased in lactation hyperthyroidism and in diseases producing fever or an increase in metabolism Hence to insure an adequate intake one would have to consider the normal requirement, the amount lost or excreted, alterations in metabolism due to disease, and the previous nutritional state of the individual

For children under 10 years of age 1 mg daily seems to be adequate to maintain good health

THERAPY OF THIAMINE DEFICIENCY *By Diet* Heart liver kidney, and lean pork are good sources of thiamine The *vitamin is* also present in high concentration in whole-grain cereals enriched flour, tomatoes and fresh green vegetables Dried brewers' yeast is an excellent source of this vitamin The *thiamine present in fresh yeast is not readily* absorbed because the living yeast cell wall resists digestion In addition to the ingestion of foods with a high thiamine content patients who are deficient in thiamine should eliminate from the diet all vitamin free foods particularly those high in *carbohydrates* such as pastries corn syrup candy, *corn* starch and soft drinks

By Oral and Parenteral Administration of Thiamine It should be remembered that water soluble vitamins are less adequately stored than the fat soluble group Hence signs of deficiency may occur in a few weeks

moderate oral doses of the vitamin

Studies on deficient individuals have shown that 100 to 125 mg of thiamine given orally over a period of 10 to 15 days will usually saturate a patient When the saturation point is reached the dosage can be decreased to the amount estimated as the daily requirement

The parenteral administration of thiamine in doses over 3 mg may result in the excretion of a large percentage of the dose, in spite of the subject's need for the vitamin There is no indication for injecting huge doses of thiamine chloride Repeated doses of 50 to 100 mg daily may be recovered from the urine almost in entirety if the patients are not deficient Even in deficient subjects as much as 80 per cent of a 50 mg dose of thiamine may be recovered from the urine within 4 hours The fact that this loss may be increased by the simultaneous administration of intravenous infusions and the use of mercurial diuretics suggests that thiamine is a threshold substance reabsorbed by the tubules When the vitamin is given

the solution subcutaneous injection may be quite painful. This drawback is not associated with intravenous administration The parenteral administration of thiamine in doses over 3 mg is attended by up to a 30 per cent urinary loss

Beriberi Heart Disease Congestive failure due to a deficiency of thiamine chloride and occurring as a manifestation of beriberi is uncommon, but not rare The diagnosis can now be made with reasonable accuracy according to the criteria of Weiss and others Thiamine chloride is a specific cure for the reversible manifestations of the disease Treatment has consisted of daily doses of 20 to 50 mg of thiamine given intravenously for a period of 2 weeks The dose is recognized to be excessive

Thiamine is ineffective in other forms of heart failure unless a nutritional basis exists

Other Uses of Thiamine It is well established that a deficiency of thiamine may produce a syndrome resembling neurasthenia Unfortunately, thiamine is of no value in nondeficient individuals with the neurasthenic syndrome Thiamine chloride alone is ineffective in the treatment of the neurologic manifestations of pernicious anemia It has no beneficial effect in the treatment of trigeminal neuralgia It does not relieve the symptoms of radiation sickness Patients suffering from Huntington's chorea, multiple sclerosis, lateral sclerosis disseminated encephalomyelitis, parkinsonism, or tabes dorsalis are unimproved by thiamine unless a previous deficiency was present Patients with Wernicke's disease (acute polioencephalitis) may be benefited by the use of thiamine chloride when the condition is found to be associated with chronic alcoholism and multiple vitamin deficiency Thiamine is of use in the treatment of diabetes only when it compensates for dietary restriction Large amounts of thiamine do not reduce the insulin requirement Altered carbohydrate metabolism does not increase the requirements of thiamine but the diuresis which occurs in poorly regulated diabetic patients may increase the excretion of the vitamin

Toxicity of Thiamine The oral use of thiamine even in amounts several thousand times the therapeutic dose, is said to be without toxic effect Severe reactions however, have been reported to follow injection of the vitamin into the subarachnoid space Allergic reactions consisting of nausea vomiting tachycardia nervousness, and a sense of constriction in the throat may follow the intravenous injection of thiamine and are thought to be the result of a *specific* sensitivity *Induced* sensitivity to the vitamin may result from the repeated injection of thiamine In sensitive individuals, the intramuscular or intravenous injection of thiamine may be followed by nausea, sneezing vasodilatation urticaria, cyanosis, and even death In such instances death is apparently due to anaphylactic shock.

In allergic individuals, particularly those who have received injections of thiamine previously, intradermal tests should always be done before thiamine is given intravenously The oral administration of thiamine

5 mg 10 mg and 50 mg Thiamine hydro chloride tablets for oral use are usually available in doses of 1 3 5 and 10 mg

DAVID CAYER

VITAMIN B NIACIN DEFICIENCY

Pellagra Niacin is present in all living cells It occurs in tissues as the amide and is an essential part of co enzymes 1 and 2 It functions in glycolysis and the intracellular respiratory function of all cells It serves to transfer hydrogen to other respiratory catalysts forming carbon dioxide and water and releasing energy

Pellagra is a well recognized clinical syndrome which is due to malnutrition and which can be corrected or prevented by the ingestion of a sufficient quantity of good protein or in most instances by sufficient niacin

ABSORPTION AND STORAGE OF NIACIN Niacin and its amide are readily absorbed unchanged from the normal gastro intestinal tract and from parenteral sites of injection The principal excretory product N[1]methyl niacinamide is formed in the liver and can be found in the urine There is experimental evidence of niacin synthesis in the bowel which persists even when sulfonamides are given The effects of oral penicillin and streptomycin on the synthesis of this vitamin are not yet known

Niacinamide is present in small amounts in all living cells There are no special sites of storage in the body although higher quantities are found in the liver and adrenal glands than elsewhere

REQUIREMENTS OF NIACIN *The minimal* daily requirement of niacin is difficult to estimate It is altered by numerous factors which include the activity of the individual the level of protein consumption the quality of protein in the diet the presence of pellagragenic substances the caloric intake the ingestion of corn and the extent of bacterial synthesis in the bowel

Niacin deficiencies which occur in persons eating large quantities of corn are due not to the lack of a niacin precursor but to an amino acid imbalance with a relative lack of tryptophane which results in an increased demand for niacin The presence of the niacin precursor and a protein which furnishes a physiologically balanced amino acid mixture on digestion accounts for the pellagra preventive properties of such foodstuffs as milk and eggs which are almost devoid of niacin The increased demand for niacin in persons ingesting large amounts of corn is thus due to the large quantity of tryptophane *deficient protein and the* unbalanced amino acid mixture which increases the demand for niacin

The National Research Council recommends 18 mg of niacin daily for a moderately active man weighing 70 kg This recommendation allows a margin of safety and a smaller intake does not imply that the diet is deficient Pellagra is rare where wheat or rice even polished rice is the chief cereal of the diet although as little as 5 mg of niacin per day may be ingested as such Persons eating milk eggs leafy green vegetables and little corn are protected by 12 to 15 mg per day Where corn is the staple food 25 mg of niacin per day may be required

It is probably best for the present to adhere to the recommended daily allowance although the figure is high and the requirements are probably less than 10 mg per day in most instances The influence of disease on the niacin requirement is not definitely known although it is probably increased by illness

THERAPY *By Diet* The best form of treatment for pellagra is to provide the patient with a diet which contains adequate amounts of both niacin and pellagra preventing foods These foods consist of any animal liver lean meat turnip greens spinach, green or black *eyed peas tomatoes yeast and bran* Peanuts and peanut butter are good sources of niacin eggs and milk though low in niacin content are important because of the quality of the protein supplied The diet should include a quart of milk daily 4 oz of fresh lean beef liver canned salmon chicken or lean pork and flour or bread to which niacin has been added The food should be given at regular and frequent intervals and special care taken to see that it is eaten When diarrhea is present symptomatic control may be helpful in increasing the absorption of niacin

By Oral and Parenteral Administration of Niacin Adequate amounts of niacin properly administered are highly specific for the

clinical manifestations of pellagra, and usually result in prompt and often dramatic improvement The ulceration and soreness of the mouth and tongue, the mental symptoms, and the dermatitis, anorexia, and diarrhea usually show evidence of regression in 2 to 4 days During this period symptomatic treatment, including special oral hygiene, therapy of infected skin lesions, control of excessive peristalsis, and correction of dehydration, should be begun

The multiple factors which probably produce the deficiency, as well as the known difficulty of saturating pellagrins with niacin, seem to justify the use of large doses over a long period of time (3 to 4 months) Cures can be produced with 50 to 100 mg per day by mouth, although cases requiring 300 to 500 mg per day have been reported Spies and his associates have recommended as much as 500 mg per day, given in divided doses They feel that the higher doses have greater efficacy The possibility of concomitant fatty infiltration of the liver in pellagra (and in alcoholic cirrhosis) and the potential damage which can result from excessive doses of niacin should be considered

The administration of niacin by mouth or parenterally is often followed by flushing and a burning, tingling sensation of the skin The reaction is harmless, and larger doses do not increase the severity of symptoms They can be reduced by administering the drug with or after meals Since niacinamide is equally effective and eliminates the unpleasant side effects, it is the preferred form of the drug for administration by any route When liver damage is present, use of the amide is probably indicated

Since multiple deficiencies are likely to be present, a supplementary intake of other B complex vitamins, in addition to a good diet, is a necessary adjunct in the treatment of active pellagra In niacin deficiencies the time required to produce saturation with the vitamin is probably longer than that required in uncomplicated thiamine or riboflavin deficiencies, and longer periods of therapy (months) are therefore [illegible]

[illegible] day) is of value Dried brewers' yeast is a rich natural source of niacin As much as 100 gm per day are suggested This may be given in divided doses in milk or tomato juice Fresh bakers' yeast is of little value

INFANTILE PELLAGRA In African infants and children with a syndrome of malnutrition which resembles pellagra, Gillman and Gillman state that massive doses of B complex vitamins administered orally or paren-

[illegible] place in the liver and produce metabolic disturbances which can no longer be corrected by vitamins administered alone or in combination with lipotropic factors They feel that large amounts of niacin are contraindicated in the treatment of severe infantile pellagra They found the use of ventriculin (5 gm twice daily by mouth), in addition to a good diet (without supplementary vitamins), to be more effective than liver by injection or diet plus vitamins If ventriculin was not available, liver extract by injection was the treatment of choice

Other Uses of Niacin The vasodilating effect of niacin has been the basis for its use in the treatment of myalgia, arthritis, Menière's syndrome, coronary artery disease, fibrositis, and headache The drug must be [illegible]

[illegible] nary vasoconstriction and should be used with caution The efficacy of niacin therapy in these conditions is still doubtful

A complete list of disorders which have been reported to respond favorably to niacin is not worth while, since in most instances further study has failed to confirm early claims The efficacy of niacin in clearing up the mental symptoms of pellagrins has led to the use of this vitamin in other forms of mental disease A beneficial effect in the encephalopathy of alcoholics occurs only if a niacin deficiency exists The chief indication for niacin therapy is in the prevention and therapy of deficiency states

Toxicity of Niacin The toxicity of niacin is low The most important single effect of the drug is the transitory vasodilatation, which is accompanied by a sensation of heat, tingling, and itching, and occasionally by urticaria Nausea, diarrhea, dizziness, and vertigo occur infrequently The effects are

transitory and do not occur when the same dose is given after meals or when the amide is administered In normal individuals derivations of niacin are relatively innocuous

Preparations of Niacin Sterile solution of 100 mg of niacin in water for parenteral use

Niacinamide for parenteral use in doses of 100 mg in 1 cc and 100 mg in 2 cc

Niacin (U S P) tablets—25 mg 50 mg and 100 mg

Niacinamide (U S P) tablets—25 mg and 50 mg

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VITAMIN B RIBOFLAVIN DEFICIENCY

Riboflavin is an essential constituent of oxidative enzymes and functions in cellular respiration

Deficiencies of riboflavin are considered by some observers to be widespread and particularly prevalent in the South However the wide distribution of riboflavin in plant and animal tissues would suggest that clinical deficiencies of riboflavin should be uncommon In all probability cheilosis and vascular invasion of the cornea which are often regarded as pathognomonic of ariboflavinosis are more often expressions of other deficiencies or are nonspecific

Absorption and Storage of Riboflavin Riboflavin when ingested or when given in small parenteral doses is absorbed easily and apparently is retained according to the needs of the patient It is synthesized in significant amount by bacteria in the bowel and may not be a dietary essential under all conditions The synthesis is less susceptible to interruption by sulfonamide therapy than is that of thiamine

The reserves of riboflavin are not great ut they are less rapidly depleted than those f thiamine Riboflavin stores in the normal dividual who is placed on a deficient diet e depleted slowly during a period of as ng as one month Thus a patient whose ake is limited for less than 2 or 3 weeks uires no more riboflavin than enough to er his daily requirement Since the stor of riboflavin is dependent on an ade- e protein intake protein must be nistered to promote the storage of the avin given Excess riboflavin is excreted urine unchanged

Requirements of Riboflavi agreement has still not been reac ing riboflavin requirements in ma states that an intake of 0 35 mg calories does not meet "requiremen however studied normal young m diets were limited to 0 31 mg of per 1000 calories (the daily diet calories contained an average of ab mg of riboflavin) and found no il In a group of subjects maintained 2 on a daily diet of 2000 calories cont 0 7 mg of riboflavin none of the c cutaneous or lingual signs of ariboflav developed The National Research Cou however proposes 0 9 mg per 1000 cal as the minimum daily requirement fo moderately active adult male weighing kg

Prophylaxis and Treatment of Rib flavin Deficiency BY DIET Prophylaxis an treatment consist in making available to th patient an adequate supply of the vitamin Dietary sources of riboflavin are liver lean meat eggs milk cheese leafy green vegetables dried yeast (1 oz daily added to cereal fruit juice or milk) green peas enriched flour and butter The riboflavin in live yeast is poorly absorbed

BY ORAL OR PARENTERAL ADMINISTRATION OF RIBOFLAVIN Well developed riboflavin deficiencies should be treated until the symptoms clear up with oral doses of 1 to 2 mg of riboflavin given three times daily in addition to an adequate diet It is important t remember that many of the signs onc thought to be pathognomonic of riboflavin deficiency are not specific and that deficiencies of niacin and other members of the B complex may also be present In such cases the symptoms will not disappear until full and adequate therapy with multiple vitamins is instituted The treatment of corneal ulcers and infiltrations with riboflavin is rapidly effective in a matter of days when the lesions are due to the specific deficiency

Occasionally the parenteral administration of riboflavin is effective when oral administration is not Improvement will usually follow intramuscular injections of 1 mg of riboflavin given daily for 3 to 4 days Deficient subjects will retain up to 75 per cent of a 1 to 2 mg dosage given parenteral Normal or saturated

to 100 per cent of such a dose in the urine unchanged the riboflavin gives the urine a deep yellow color In patients with severe riboflavin deficiencies a total dosage of 40 to 50 mg divided into small oral doses given several times a day will saturate the patient in approximately 10 days unless other complicating disorders have radically altered the metabolism

Toxicity of Riboflavin No toxic effects from enormous doses of riboflavin have been noted in human beings the excess is excreted in the urine within several hours

Preparations of Riboflavin Riboflavin tablets (U S P) are available in 1 and 5 mg sizes A sterile solution of riboflavin in water (1 mg in 2 cc 5 mg in 1 cc) is available for injection this solution may contain other suitable agents to increase solubility such as urea or niacinamide Riboflavin readily precipitates out of solution as dark crystals the precipitation is accelerated by light

DAVID CAYER

reduced form by the kidney makes it possible to determine the point at which saturation of the body stores is reached Ascorbic acid is also excreted in sweat and milk

The body stores of vitamin C are not large In otherwise normal individuals who are given a diet containing no ascorbic acid symptoms of scurvy appear within 5 to 6 months Thus patients who are unable to take foods containing vitamin C or who have been on a previously deficient diet should be given ascorbic acid Adequate protection is probably afforded for at least 4 months by normal body stores In all proba [illegible] nonths

[illegible] 'imates of the minimal daily requirement of vitamin C for an otherwise healthy adult range from 25 mg to 100 mg per day The standard [illegible]

VITAMIN C DEFICIENCY

Scurvy Ascorbic acid (vitamin C) is generally considered to participate in oxidation reduction reactions in the body and in cellular respiration although its precise function is unknown Chemically it is a strong reducing agent and hence is quickly and easily oxidized When it is absent from the body normal intracellular "sticky substance is not formed and the clinical manifestations of scurvy appear Vitamin C is essential for life since it is not synthesized by man a continuous source of supply is necessary to maintain health Prolonged depletion produces the clinical syndrome of scurvy and ultimately results in death

Scurvy is now primarily a problem of infancy although it may occur in aged individuals subsisting on diets markedly deficient in vitamin C

ABSORPTION AND STORAGE OF ASCORBIC ACID Ascorbic acid either synthetic or natural is rapidly absorbed from the intestines after ingestion It is stored in many organs particularly the adrenal cortex and liver In the presence of a vitamin C deficiency a [illegible]

and ensure saturation

Scurvy has been produced experimentally by limiting the intake of ascorbic acid to 10 mg per day Similar studies have indicated that a daily diet containing 25 mg of vitamin C or possibly less will protect against scurvy and ensure wound healing On dosages of 25 to 75 mg of ascorbic acid per day tissue reserves are increased and saturation of body stores usually takes place An intake in excess of 75 mg per day usually results in saturation and rapid excretion of the excess ascorbic acid in the urine Where the requirements are increased as for example in lactating women as much as 150 mg per day may be necessary The difficulty in producing saturation of the body stores in patients with febrile diseases leukemia or hyperthyroidism probably indicates a greater destruction of this vitamin and increased need for it in these patients

There is no indication that it is necessary or beneficial to maintain complete saturation if a constant daily intake is assured

PREVENTION AND TREATMENT OF SCURVY *By Diet* The prevention and treatment of scurvy consist in providing the individual with sufficient amounts of vitamin C The

daily requirement could be supplied in entirety by 8 oz of freshly prepared citrus fruit juice or 1 pt of canned tomato juice An 8 oz. glass of orange juice plus a similar amount of *fresh* tomato juice will supply 150 mg of vitamin C Fresh vegetables provide a stable source Cabbage, turnips, baked potatoes, and tomatoes are excellent sources, as are cantaloupes and orange, tomato, lemon, or grapefruit juice The advantage of citrus fruits is that they are regularly eaten raw

Ascorbic acid is destroyed by oxidation, but not by heat It should be remembered that fruit juices which are prepared and allowed to stand, particularly if uncovered, in iron or copper receptacles, depreciate rapidly in vitamin content This depreciation occurs whether the juices are refrigerated or not, though cooling slows the rate of oxidation In addition, the ascorbic acid in vegetables is reduced by exposure to light and by prolonged storage whether refrigerated or not The addition of soda to vegetables during cooking reduces the vitamin C content materially, since this vitamin is destroyed more rapidly in an alkaline medium Achlorhydria and antacids may also affect the destruction and stability of ascorbic acid in the bowel, and may reduce the amount absorbed

By Oral or Parenteral Administration of Ascorbic Acid Patients with frank scurvy can be saturated with vitamin C by doses of 100 mg given by hypodermic daily for 7 to 10 days A larger dose of 500 mg of ascorbic acid may be given orally three times a day For most patients deficient in ascorbic acid a total of 1500 mg will produce saturation of the body stores Where a prolonged deficiency of ascorbic acid has preceded treatment, 1500 mg daily for 2 or 3 days may be required The tourniquet test for capillary fragility may be used as a clinical test of response to therapy, the signs of increased capillary fragility disappear within 24 hours after the body requirements for vitamin C have been met

Ascorbic acid is water soluble and is suitable for parenteral injection Occasionally clinical scurvy may not respond to vitamin C given orally, but will disappear following intramuscular or intravenous administration of the vitamin It acts as a threshold substance and is excreted in the urine Since the intravenous injection of a large dose of vitamin C elevates the plasma level more than an oral dose of similar size a greater amount is excreted

Crystalline ascorbic acid may be dispensed in tablet form in dosages of 25 mg per day, or dissolved in propylene glycole to supplement the formulas of young infants unable to take fruit juices Where it cannot be taken orally, intramuscular injection is more economical than intravenous administration, since less is lost through the kidneys following the injection

Exceptions to the above statements regarding the dosage and quantity necessary for saturation may be found in patients having leukemia or certain metabolic disorders and in those receiving intravenous fluids or diuretics which produce excessive excretion Otherwise, once the body has been saturated, 75 mg of ascorbic acid daily is more than enough

Other Uses of Vitamin C The Sippy diet and other bland diets used for gastro intestinal disturbances are frequently low in vitamin C In addition, these patients may complain of digestive disturbances following the ingestion of fruit juices In such individuals the administration of the purified vitamin concentrate may be necessary to make up for the dietary inadequacy

Anemia There have been numerous reports of hematologic studies made on patients with naturally occurring or experimentally induced scurvy Anemia, which may be normocytic or macrocytic, may occur In general, however, scurvy and anemia do not necessarily coexist Constant blood loss or lack of iron and dietary essentials other than ascorbic acid usually accounts for the anemia In some patients, however, after all other factors have been corrected hematologic and clinical improvement will occur only when crystalline vitamin C is administered In these patients a reticulocyte response will be noted in 5 to 8 days It must be emphasized that these patients all show clinical signs of an ascorbic acid deficiency

There is no apparent relationship between iron and ascorbic acid in the synthesis of hemoglobin The concomitant administration of iron does not prevent the utilization of

ascorbic acid, and an excess of vitamin C is of no value in the therapy of anemias not associated with scurvy

Wound Healing In severe scurvy, wound healing is delayed or absent Such a degree of depletion in the average surgical patient, however, is most unlikely In patients in whom no clinical evidence of a vitamin C deficiency can be demonstrated and in whom demonstrable levels of vitamin C can be found in the blood plasma there is no decrease in wound healing

alone

It has been reported that the simultaneous administration of 250 mg of ascorbic acid with mercuhydrin will decrease the toxicity of the latter without affecting its diuretic action It has also been reported that vitamin C counteracts the toxic action of arsenicals in man without impairing their therapeutic efficacy This effect is said to be most favorable when both the arsenical and vitamin are injected in the same solution There remains however, some difference of opinion as to the value of ascorbic acid as a detoxifying agent

Gingivitis The diagnosis of a vitamin C deficiency on the basis of gingivitis alone is unwarranted as is the attempt to cure all types of gingivitis with vitamin C

In general it may be said that ascorbic acid has little usefulness except in the prevention and cure of scurvy

Toxicity of Vitamin C There is no evi-

tablets (U S P) containing 25 50 and 100 mg are available for oral administration Ampules containing 100 mg dissolved in 10 cc of sterile distilled water may be had for intramuscular and intravenous use

DAVID CAYER

VITAMIN D DEFICIENCY

The name "vitamin D" is given to a number of sterols which are capable of preventing and healing rickets and producing normal mineralization of bone Vitamin D promotes the intestinal absorption of calcium and phosphorus, and maintains the blood concentrations of these substances necessary for the normal calcification of bone The vitamins D are formed in or out of the body, before or after ingestion, from the inactive sterol by ultraviolet irradiation or other physical processes

Although many vitamins D are known at the present time, vitamins D_2 and D_3 are the most important in man and have almost equal therapeutic powers Vitamin D_2 (calciferol) is the active substance in viosterol, drisdol and many other potent antirachitic preparations It is formed by the irradiation of ergosterol and contains 40 000 international units of vitamin D per milligram Vitamin D_3 (activated 7 dehydrocholesterol) is the natural vitamin produced in the human skin by exposure to ultraviolet rays

Absorption and Storage of Vitamin D Vitamin D is absorbed from the gastro intestinal tract from parenteral sites of injection, and through the skin Normally, a considerable amount of the vitamin is obtained from exposure of the body to sunlight Apparently the vitamin D formed in the skin is absorbed into the blood stream Ingested vitamin D is absorbed largely from the small intestine Absorption is increased by the presence of moderate amounts of fat and the presence of bile Vitamin D is not well absorbed by many persons with obstructive jaundice unless bile salts are also administered

There are no special sites of storage for vitamin D in human beings The vitamin is probably stored to some slight extent by all body tissues There is evidence that the vitamin is stored in the body for 3 to 6 months following the administration of large amounts Some vitamin D is metabolized, some is excreted through the intestine (25 per cent) It is also excreted in milk

Requirements of Vitamin D FOR CHILDREN The requirements for vitamin D depend on the rate of growth, the amount of exposure to sunshine and the foods eaten The daily requirement of children from birth up to 15 years of age probably varies between 400 and 800 international units The prophylactic requirement for premature infants is thought to be as much as twice that of full term infants until the second year of

life, because of the more rapid rate of growth A daily intake of 500 international units will usually protect full term infants and young children Higher allowances up to 800 international units, provide a wider margin of safety Where ample exposure to sunshine is obtained, smaller amounts of vitamin D are required in the diet

For Adults The adult's requirement for vitamin D is unknown It is probably 300 to 400 international units per day A supplement of 700 international units of vitamin D, in addition to an adequate calcium intake, is recommended for mothers during pregnancy and lactation The requirements for vitamin D appear to be higher at this time than at any other period

Prophylaxis The ingestion of vitamin D is required only when the human organism is not exposed to sunlight or other sources of ultraviolet rays and is thus unable to synthesize vitamin D The provitamins D which are activated by irradiation, are found in many plants and animals Vitamin D, however, is scarce in nature The foods which contain the greatest amounts are eggs butter milk, and liver The fish liver oils are the best source of this vitamin Since they may vary considerably in antirachitic potency the dose must be adjusted according to the content of vitamin D

In regions where ultraviolet irradiation is scarce during the winter months, many children are unable to produce their own vitamin D They must be given supplementary amounts of the vitamin to prevent rickets Cod liver oil is the best known source of vitamin D although its concentration is below that of many other fish liver oils *In doses of equivalent units*, percomorph oil cod liver oil viosterol, and crystalline vitamin D are equally effective in the prevention and treatment of rickets

Normal Full-Term Infants Vitamin D, 300 to 400 units, per day supplied by evaporated or irradiated milk is sufficient to prevent rickets in most full term, normal infants By the end of the second week, 200 *units* of vitamin D per day should be given, and the dose increased *to* 400 units by the end of the first month *Parks recommends* even greater *amounts* 800 to 1200 units, for the remainder of the first year, and 800 units per day throughout the second year In most instances this higher amount will be well tolerated, and can be given in any of the accepted preparations of vitamin D It is best to give this by dropping it on the tongue or directly into the mouth during feeding If it is given in milk, a preparation miscible with water should be used, since the oil may remain on the sides of the bottle

Premature Infants *Premature infants are highly susceptible to rickets The requirements for such infants are higher than those* for a full term baby *As a rule, 800 to 1200* units of vitamin D per day will prevent the clinical manifestations of rickets in premature infants, although in some instances the daily intake may have to be raised to 20,000 to 30,000 units for a time The individual requirements govern the dosage Calcium salts should be given in addition to vitamin D at the onset of treatment

Single Massive Dose Therapy Vitamin D can be *demonstrated in the circulating* blood 2 to 3 months after a single oral dose of 200 000 units Following the administration of daily doses, levels of vitamin D in the blood serum remain normal for 3 to 6 months For this reason, some have advocated the use of single massive *doses of* vitamin D, for which they claim the following advantages (1) *They eliminate* the usual daily dietary supplement, and are therefore timesaving, only two oral doses per year, one during the winter and one in the spring months, are required (2) Loss by regurgitation of the feeding is less likely to occur

Some investigators feel that single large doses of vitamin D should be administered parenterally to obviate the possibility of poor absorption or improper administration They also advise parenteral administration when infants are premature, when intestinal absorption is poor, or when intestinal disturbances are present.

The size of the dose *depends on the age and weight of the infant and the time interval between doses Infants receiving* a single dose of 300 000 or 400 000 units of vitamin D will not develop rickets for a period of 8 weeks following injection Two hundred thousand units, however, cannot be depended upon as a single prophylactic dose

Two general plans of treatment are recommended

(1) At the age of 1 month 50 000 units of vitamin D are given 50 000 units at the age of 2 months and 600 000 units after 3 months The first two doses are administered with the baby's formula The third is given with precooked cereal in divided doses 24 hours apart A repeat dose of 600 000 units may be given from 3 to 6 months later de pending on the needs of the infant the season and the clinical findings When an infant is obtaining adequate sunshine the repeat dose may be deferred until the onset of winter A dose of 600 000 units may then be given two or three times during the next year

(2) A dosage of 1000 units of vitamin D is given each day until the age of 2 months Then 600 000 units is given and this dose is repeated 4 months later In October and the following January 600 000 units can then be given

Vitamin D is a powerful and dangerous drug and the administration of massive doses requires careful supervision by the physician The margin of safety is great however unless toxic levels are maintained over a period of time In children with nephritis polycystic kidneys or pyelone phritis the use of large doses of vitamin D predisposes to metastatic calcification in the kidneys and other organs and is therefore contraindicated Repeated examinations of the urine blood pressure and blood calcium should be made during treatment

Rickets Vitamin D concentrates should be used in the treatment of rickets since pre mature infants may require as much as 10 000 to 20 000 units per day In the majority of cases however 1200 units per day will suffice In rare instances the use of oral or intramuscular doses as high as 600 000 units may be necessary Effective treatment usually produces roentgenographic evidence of healing within a period of 2 weeks Such treatment must include an ample intake of calcium and phosphorus Th s is supplied when an adequate amount of milk is given (1 to 1½ liters) If necessary supplementary calcium may be given as calcium gluconate lactate or dibasic phosphate (1 gm three times a day)

Cases of refractory" rickets are occasion ally seen beyond infancy The usual dose of vitamin D is ineffective in curing these chil dren and enormous amounts are necessary Treatment should be begun with daily doses of 500 000 to 1 000 000 units of vitamin D and continued until evidence of healing is noted the dose should then be reduced to lower levels

The hypocalcemia associated with in stances of "renal" rickets is secondary to disturbed renal function It is accompanied by elevation of the blood phosphates and nonprotein nitrogen and should not be treated with vitamin D

Osteomalacia This condition is often termed "adult rickets It is uncommon in the United States Treatment is similar to that of rickets Therapeutic doses of vitamin D (7500 to 15 000 units daily) are recom mended along with a generous intake of calcium (1 5 gm. daily)

Senile Osteoporosis The relation of this disorder to osteomalacia and the efficacy of vitamin D in its treatment are still unde cided Hormonal influences and a diet defi cient in proteins may be contributing

caution in regulating the dosage and dura tion of treatment

Hypocalcemic Tetany Tetany is often associated with rickets and may be due to inadequate dietary intake or poor intestinal absorption of calcium and a deficiency of vitamin D The immediate symptoms are best controlled with 5 to 20 cc of a 5 to 10 per cent solution of calcium gluconate given slowly by vein or intramuscularly Vitamin D and a diet high in calcium are useful in the subsequent treatment of hypocalcemic tetany A high intake of vitamin D (100 000 to 500 000 units per day) will increase cal cium absorption Calcium lactate or calcium gluconate may be dissolved in water or milk and given in doses of 1 to 2 gm three times a day Acid producing salts such as am monium chloride (1 to 2 gm three times a day) or dilute hydrochloric acid are also of value since calcium is ionized and absorbed better in an acid medium Where laryngo-spasm is marked morphine (1 mg per 5 kg of body weight for infants) may be admin istered by hypodermic or avertin (50 to 100 mg per kilogram of body weight) may be

given in a 1 25 per cent solution as a retention enema

The treatment of hypoparathyroid tetany with dihydrotachysterol (A T 10) a substance related to vitamin D *is discussed elsewhere*

Other Conditions Large doses of vitamin D have been employed in the treatment of arthritis Editorial comment from the *Journal of the American Medical Association* sums up the present opinion Critical examination of the reports on the value of vitamin D in the treatment of chronic arthritis reveals little to warrant the belief that the beneficial *effects claimed are specific*

The use of vitamin D in tetany due to causes other than hypocalcemia in the treatment of psoriasis and acne and to induce calcification in trichinosis is of dubious value

Toxicity of Vitamin D Individual tolerance to vitamin D varies but there is little danger of toxic reactions if reliable preparations are given in amounts less than ten times the preventive antirachitic dose In most instances the margin between therapeutic and toxic levels is large The vitamin D preparations known to have produced toxic effects include fortified cod liver oil irradiated ergosterol and electrically activated vaporized ergosterol Instances of vitamin D poisoning in infants receiving 20 000 to 40 000 international units daily over a period of several months have been reported A daily dose of 20 000 international units per kilogram of body weight *is usually considered* as the minimum toxic dose for human beings Toxic reactions are usually due to irradiated ergosterol given in high concentration *toxic effects from cod liver oil are unlikely*

The most frequent symptoms of vitamin D poisoning are anorexia nausea vomiting occasional diarrhea polyuria muscular weakness lassitude headache and depression *If the vitamin D is continued it may* produce skeletal decalcification calcification of the kidney tubules and other organs and death When signs of vitamin D intoxication are detected the dose must be reduced or *the drug withdrawn* As might be anticipated the danger is greatest in children where the dose of vitamin D is larger in proportion to body weight and symptoms may not be detected early

Preparations of Vitamin D FORTIFIED FOODS The vitamin D content of some natural foods has been increased by artificial means The foods are fortified with vitamin D either by feeding the vitamin D and its precursors to the animal which provides the food stuff or by adding concentrates directly to the food particularly bread cereal and milk Foods fortified with vitamin D are labeled as such

NATURAL AND SYNTHETIC PREPARATIONS A *partial* list of commonly used natural and synthetic preparations of vitamin D appears below It is important to remember that natural oils contain vitamin A in high concentrations whereas preparations of artificially activated vitamin D do not unless they are enriched

The vitamin D content of the better *cod liver oils is* two to three times the *U S P* requirement One teaspoonful (4 gm) will supply between 340 and 1000 units depending on the potency *All doses must be administered in terms of the potency of the preparation used* The more potent preparations may be dispensed in proportionately smaller amounts

The potency and dose of *cod liver oil concentrates* vary with the preparation

Cod liver oil with viosterol contains 850 units of vitamin A and 360 units of vitamin D per gram The daily recommended dose for normal full term infants and adults is 2 to 4 cc for premature infants and the treatment of rickets 8 cc

Percomorph oil is a rich source of vitamin D It is put out in varying concentrations The preparations are labeled according to the number of units per gram

Viosterol contains 10 000 units of vitamin D per gram One cubic centimeter equals approximately 0 9 gm The recommended daily dosage for full term infants and adults is 5 drops for premature infants or the

for normal full term infants and adults is 5 drops (2 to 3 drops if given in fortified milk) for premature infants or the treatment of rickets 15 to 20 drops

DAVID CAYER

VITAMIN K DEFICIENCY

The term "vitamin K" is applied to that group of compounds which can be utilized

fested by a tendency to hemorrhage and a lowered prothrombin level of the blood

Absorption and Storage of Vitamin K The naturally occurring vitamin K is fat soluble and the presence of bile salts is required for its absorption Where bile is absent from the intestine as in obstructive jaundice or biliary fistulas hypoprothrombinemia is common

Since assays of tissues reveal that little vitamin K can be stored the time required for depletion may be only a matter of days The synthetic precursors of vitamin K are not stored but some are absorbed from the bowel in the absence of bile salts

Requirements of Vitamin K The exact requirements of vitamin K for human beings are not known They are probably quite low however and 1 to 2 mg of pure vitamin K if properly absorbed and utilized will correct a deficiency Prothrombin is formed rapidly by the liver and a deficiency can be corrected in a matter of hours

Sources of Vitamin K Two naturally occurring vitamins K are known Vitamin K is present in green leaves and is widely distributed in plants Spinach cabbage cauliflower and kale are good sources Fruits are poor sources Vitamin K_2 is synthesized by a variety of bacteria from almost any food in the human intestine *Escherichia coli* produces the vitamin even in a simple culture medium Yeast however does not contain it

Prophylaxis and Treatment of Conditions Characterized by Hypoprothrombin

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additional vitamin K is of no value

In the treatment of hypoprothrombinemia frequent laboratory determinations of the prothrombin content of the blood must be used as a guide since the levels may drop acutely Satisfactory simple micro and macromethods requiring only minutes to run are available The prothrombin time in seconds varies with the local standard and is usually reported as the percentage of normal Bleeding usually is manifested at 20 per cent In the absence of liver damage a reduced prothrombin time is an indication of a depletion of vitamin K stores

Hemorrhagic Disease of the Newborn If the mother is obtaining an adequate diet sufficient vitamin K is absorbed to provide the fetus with normal prothrombin levels In the winter months when the mother s diet may be low in vitamin K the fetus may not store enough of the vitamin to be protected during the first week of postnatal life The administration of sulfonamides or salicylates to the mother may also depress the prothrombin level of the baby The use of mineral oil by the mother probably interferes little with the absorption of vitamin K

A deficiency of vitamin K in the infant is characterized by bleeding during the trauma of delivery and during the first week of life and is accompanied by a low concentration of prothrombin in the blood Within 12 hours after birth the prothrombin often begins to drop progressively if the stores of vitamin K are not replenished When hemorrhage occurs the decrease in circulating prothrombin is even more marked When the infant s dietary source is derived solely from milk and bacterial synthesis in the bowel has not yet become established dangerously low levels may occur if the vascular system is uninjured however bleeding may not be manifested

Opinion concerning the prophylactic use of vitamin K varies Some clinicians recommend the parenteral administration of vitamin K to all mothers during labor and to the babies after birth in an effort to provide maximal protection to the baby Others feel that the low prothrombin levels found in newborn infants are physiologic and tend to be misleading They feel that the low incidence of hemorrhagic disease of the newborn (less than 0 5 per cent of all infants) makes it foolish to waste vitamin K on the remaining 99 5 per cent particularly since the water soluble preparations offer a prompt means of treatment for those showing hemor

rhagic tendencies Since the possibility exists, however, that a low prothrombin level in a newborn infant may result in uncontrollable bleeding if a vascular injury does occur during delivery, the prophylactic administration of vitamin K to the mother seems justified Investigators are not agreed on the optimal time of administration before labor and the correct dose Since there is no evidence of a cumulative effect it would seem useless to give the drug for more than a week prior to delivery If the mother has received no vitamin K, a dose of 1 mg of menadione (a fat soluble synthetic precursor) given orally each day during the last week of gestation or 2 to 5 mg of a water soluble preparation given by mouth 2 to 5 hours before delivery is adequate Intramuscular injection of 2 to 5 mg of an aqueous preparation is equally satisfactory The parenteral administration of vitamin K to mothers in labor brings the prothrombin content of the blood in both mother and infant to normal levels in 1½ to 4 hours The usual fall in prothrombin between the second and fifth day of life is not present when adequate vitamin K is given to the mother during labor or to the infant after birth

When bleeding occurs in a newborn infant, 2 to 5 mg of a water soluble preparation should be injected intramuscularly or intravenously without waiting for a laboratory diagnosis of hypoprothrombinemia The need for additional therapy can be decided later by determining the prothrombin time It is important that newborn infants requiring surgery be given vitamin K preoperatively

Bleeding Due to Inadequate Absorption of Vitamin K In the absence of bile salts, absorption of natural and fat soluble vitamin K is faulty, and a fall in prothrombin may result Hence low levels should be anticipated where obstructive jaundice or biliary fistulas exist When the reserve supply is depleted, the fall in prothrombin may be rapid A single prothrombin determination indicates only the circulating prothrombin level It gives no information as to the amounts stored or the body's ability to maintain a normal blood level Thus a jaundiced patient whose prothrombin time was normal before operation may begin bleeding shortly after operation Factors which may be responsible for the depleting of vitamin K stores include the loss of blood, the reduction of hepatic function caused by anesthesia, and the subsequent anorexia, and limitation of the diet, the preoperative use of drugs which inhibit the synthesis of bacterial flora may also play a part

Hypoprothrombinemia due to the lack of bile may be prevented or treated by the oral administration of menadione and bile salts or a water soluble preparation of vitamin K orally With the latter simultaneous administration of bile salts is not necessary Two to 5 mg of menadione given orally with bile salts will maintain a normal prothrombin time for 2 to 3 days Where more rapid therapeutic results are desired intramuscular injections of one of the water soluble preparations is advisable These have 50 to 70 per cent of the vitamin K activity of a similar amount of menadione If intramuscular injections are used 4 mg of the water soluble substances given every 2 or 3 days is sufficient If given intravenously, 2 mg daily is an adequate dose If massive bleeding or shock becomes apparent, whole blood or plasma should be given to compensate for the time lag in the restoration of prothrombin levels

Gastro intestinal Disorders The hypoprothrombinemia which accompanies intestinal disturbances is due to faulty absorption of vitamin K It is particularly apt to occur in instances of steatorrhea In such patients the parenteral use of vitamin K is indicated Two milligrams of menadione or its equivalent per day are usually adequate The need for larger doses or prolonged treatment can be ascertained by determination of the prothrombin level and will depend on the response of the steatorrhea to other treatment

Since prothrombin is synthesized in the liver, primary parenchymatous disease of the liver diminishes the synthesis and storage of the vitamin Effective therapy in such instances must be designed to treat the hepatitis Where such efforts are successful, the production of prothrombin is rapidly restored In the less severe forms of hepatitis the prothrombin rarely drops to critical levels The use of vitamin K in these patients is of little help Vitamin K is probably not indicated in the treatment of cirrhosis except where blood loss has already occurred

In such cases it may be helpful in preventing a drop in the blood prothrombin level secondary to the hemorrhage

Decrease in Prothrombin Formation* Dicumarol retards the synthesis of prothrombin producing a fall in prothrombin levels within 2 to 3 days In patients receiving dicumarol, synthetic vitamin K was first noted to produce little effect, but it is now

water soluble synthetic percursor) will usually cause the prothrombin time to fall to safe limits if dicumarol is discontinued simultaneously These doses of vitamin K were given without ill effects A definite lowering of prothrombin time usually occurs within 2 hours and reaches a maximum in 18 hours The need for subsequent treatment can be evaluated by determining the prothrombin time

The hypoprothrombinemia induced by salicylates can be prevented by vitamin K In general salicylates in therapeutic doses (up to 10 gm daily) produce only moderate prothrombinopenia However it is wise to administer vitamin K prophylactically to patients with rheumatic fever who are receiving salicylates or sulfonamides and in whom an operative procedure such as a tonsillectomy is being considered The dosage of vitamin K which will counteract the prothrombinopenia produced by a given quantity of salicylates cannot be accurately determined, although it is probably in the neighborhood of 1 mg of menadione for 1 gm of acetylsalicylic acid

* Recent studies by Miller Harvey and Finch question the actual value of synthetic vitamin K preparations in returning the coagulation defect produced by dicumarol to normal These observers feel that vitamin K (2 methyl-3 phytyl 1, 4 naphthoquinone) and vitamin K oxide menadione (2 methyl 1 4 naphthoquinone) are far more potent than the usual vitamin K preparations These substances may be obtained from Merck and Company and are most efficient when given intravenously in a dose of 0 5 to 1 gm No toxic effects were noted but it must be emphasized that although the danger of serious hemorrhage may be averted with the use of these drugs the danger of thrombo-embolic complications continues to be present —*Editor*

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Congenital Hypoprothrombinemia Instances of idiopathic hypoprothrombinemia in otherwise normal individuals have been reported When it occurs in females 2 to 5 mg of menadione prior to menstruation may prevent excessive hemorrhage and a further drop in prothrombin levels A daily intake of 1 mg is probably advisable as a prophylactic procedure Therapeutic doses would be necessary only where the prothrombin is below the 20 per cent level and considerable blood is lost

Other Uses of Vitamin K Vitamin K is of value in the treatment of menorrhagia only when the prothrombin is reduced

Hemorrhage occurring with blood dyscrasias or accompanying peptic ulcer may produce prolongation of the prothrombin time if vitamin K reserves are low

The assumption that prothrombin provides cellular nutrition and influences capillary permeability has led to the use of vitamin K in the management of urticaria It is of doubtful value in this condition

Toxicity of Vitamin K *Vitamin K in therapeutic doses seems to be nontoxic* Eight milligrams of menadione have been given daily by mouth to human patients over a period of 30 months without signs of toxicity Two hundred milligrams of synkayvite (a brand of water soluble synthetic vitamin K) given intravenously to normal individuals produced no ill effects The toxic dose of synthetic naphthoquinones so greatly exceeds the therapeutic dose that there is little, if any toxic reaction in routine treatment

In human beings a toxic dose of vitamin K produces vomiting and a fall in blood pressure Daily doses of 10 mg or less by mouth are entirely nontoxic, and 20 mg daily of the water soluble preparations can be given intravenously for weeks without untoward effects The drug however, was found to be irritating to the skin and mucous membrane when applied locally as an ointment In general the margin of safety between the effective therapeutic dose and the toxic dose of vitamin K is so great that it may be considered to be practically nontoxic

Preparations of Vitamin K Naturally occurring substances with vitamin K activity have been supplanted by active synthetic products

Menadione (2 methyl 1 4 naphthoquinone) is available in 1 2 and 5 mg tablets for oral use and in 1 cc ampules containing 2 mg dissolved in oil for intramuscular use

A series of related water soluble compounds has also been synthesized When given intravenously the water soluble substances with vitamin K activity quickly provide a temporary supply of vitamin K to the liver These compounds include such preparations as

Hykinone (2 methyl 1 4 naphthohydroquinone-3 sodium sulfate) available in ampules of 10 and 40 mg for intravenous use and in 4 8 mg tablets

Synkamin (4 amino 2 methyl 1 naphthol hydrochloride) available in 4 mg capsules for oral use and in ampules containing 1 mg per cubic centimeter for parenteral use

Synkavite (2 methyl 1 4 naphthohydroquinone diphosphoric acid ester tetrasodium salt) available in 5 mg tablets for oral use and in 10 cc ampules for intravenous use

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THE SPRUE SYNDROME

Successful therapy of the sprue syndrome is dependent on recognition of the origin of the varied manifestations Most clinicians group together under the diagnosis of sprue at least three separate entities (1) acute sprue (both "tropical and nontropical") (2) partially or completely refractory sprue (chronic sprue often called "nontropical sprue) and (3) steatorrhea of idiopathic origin with or without accompanying anemia Patients with any of these complexes exhibit evidences of gastro intestinal malabsorption particularly of fats and fat soluble substances Macrocytic anemia with megaloblastic arrest is present in true sprue and may accompany idiopathic steatorrhea

The gastro intestinal malabsorption may result in the development of conditioned deficiencies of calories (weight loss) protein (hypoproteinemia) vitamin K (hypoprothrombinemia) calcium and vitamin D (hypocalcemic tetany and osteoporosis) vitamin A (nyctalopia) vitamin C (scurvy) and perhaps other factors In cases of idiopathic steatorrhea anemia may be conditioned by malabsorption of hemopoietic vitamins Accordingly therapy must be directed at treatment of the anemia at correction of or compensation for the underlying absorptive defect immediate remedy of any clinically manifest or latent conditioned deficiency (such as hypoprothrombinemia or hypocalcemia) and the provision of an abundant diet to replenish the body content of depleted nutrients

The macrocytic anemia encountered in the sprue syndrome responds satisfactorily to folic acid (pteroylglutamic acid) in daily doses of 5 to 15 mg orally or parenterally Concentrated liver extract (15 units per

to 300 units is administered The recently isolated vitamin B_{12} is reported to be hemopoietically active in sprue but the optimal therapeutic dose of this new vitamin cannot be stated at this time It may approximate (in micrograms) the dosage schedule recommended for liver extract since 1 microgram of vitamin B_{12} seems to approximate 1 unit of liver extract

Maintenance therapy is frequently required for patients with sprue unless pronounced sustained dietary changes can be induced Satisfactory specific maintenance will be provided most patients by 5 mg daily of folic acid orally or by periodic intramuscular administration of liver extract in amounts sufficient to supply an average of 1 unit daily Evaluation of maintenance by vitamin B_{12} cannot be made at the time of writing

Unless acute sprue has become partially or completely refractory the gastro intestinal

manifestations are usually well controlled by folic acid or liver extract In idiopathic steatorrhea or refractory sprue these manifestations are but partially or poorly controlled by specific agents and there is a marked tendency to relapse Many of these patients are benefited by the oral administration of an agent which enhances the emulsification of fat and thereby promotes the absorption of lipids and fat soluble substances Such an agent is polyoxyethylene sorbitan mono oleate (Tween 80') which is useful in improving the absorption of fats in a variety of absorptive difficulties, including cases of the sprue syndrome The dosage of this agent which has been used is 1 5 gm with each of three meals daily

The prompt control of the accompanying *conditioned deficiencies* may be of utmost importance, particularly is this true of bleeding due to hypoprothrombinemia and of tetany The measures necessary for their treatment are essentially those employed for the same deficiencies wherever encountered Prothrombin levels will be readily restored by small parenteral doses of a vitamin K preparation such as 2 mg of menadione or by oral administration of, preferably, a water dispersible derivative of vitamin K such as menadione tablets in 2 to 5 mg dosage The tetany and osteoporosis are more difficult to control and require more prolonged therapy Acute attacks of tetany are relieved by intravenous injections of 10 cc of calcium gluconate, rebreathing may be of value for milder attacks Serum calcium levels can usually be increased slowly by the oral administration of calcium chloride, 1 or 2 teaspoonfuls of a 33 per cent solution in water with three meals daily and a vitamin D preparation some 5000 to 20,000 units daily Theoretically, water dispersible preparations of vitamin D should be the more effective In some instances the control of tetany may present a stubborn problem requiring trials of other agents, as dihydrotachysterol, which serve to promote calcium absorption and retention

Conditioned scurvy responds readily to daily quantities of 200 to 300 mg of ascorbic acid in divided doses for a few days It is rare to encounter vitamin A deficiency of the severity requiring specific measures If avitaminosis A is clearly manifest, daily administration of 10,000 to 25 000 units of vitamin A should suffice to control it, particularly if given with an emulsifying agent

The rare patient with sprue will exhibit a concomitant iron deficiency anemia due to excessive blood loss, sometimes caused by intestinal parasites Where this occurs, the administration of the usual oral dose of 0 3 gm of ferrous sulfate three times daily for a few weeks will relieve this deficiency If intestinal parasites are present, the appropriate therapy should be instituted

Adjustment of the pattern of dietary intake to provide an abundant allowance is basic in the successful therapy of the sprue syndrome No magic pattern of diet exists for treating this disease Inasmuch as the treated patient is building new body tissue has an inefficient absorption of foodstuffs generally, and has low body reserves of nutrients, it is obvious that an abundant intake of calories, protein, and protective foods is in order Initially a moderately low fat diet may be desirable in order to prevent aggravation of the existing steatorrhea The acutely ill patient may not tolerate overfeeding Frequent smaller servings should be given instead of larger quantities in the usual three meals daily With the response to specific therapy, however, it is seldom necessary or desirable to continue a low fat regime The diet should contain 100 to 130 gm of protein, a goodly portion of which should be derived from animal sources (lean meat liver, milk, eggs, cheese) Daily menus should provide a variety of vegetables (both root and leaf), fruits meats, and dairy products Frequent inclusion of organ meats (liver, heart, kidney) in the menus is desirable because of their high nutrient content Efforts should be made to persuade the patient to continue such a regimen after recovery from the acute illness

During the stages of acute illness and early remission it is desirable to permit the patient to exercise cautiously in order to reduce the possibility of thrombophlebitis or orthostatic pneumonia

The immediate treatment, therefore, of the acute case of sprue consists of specific therapy with a hemopoietic factor and correction of recognizable evidences of other deficiencies and dietary adjustment After recovery of body weight and vigor (several

months), it may be advisable to withdraw specific therapy and test the ability of the patient to maintain himself on an abundant diet alone If relapse occurs it may not become evident for a year or more, hence observation of the patient should be sustained over a period of considerable time after withdrawal of specific therapy Should evidence of relapse be detected, reinstitution of specific therapy should be made

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ANOREXIA NERVOSA

Introduction *This discussion of the treat*ment of anorexia nervosa is based on the premise that the state of starvation which characterizes this condition is secondary to a psychic disturbance and that the endocrine disturbances which occur are in turn secondary to the starvation It is apparent that this concept necessarily discredits the diagnosis of Simmonds' cachexia which is frequently made when this clinical picture is presented It is equally apparent that the widespread acceptance of the concept of Simmonds' cachexia has retarded general recognition of the true basis for this symptom complex The manifestations of starvation which are observed in anorexia nervosa are not associated with the complete and permanent anterior pituitary insufficiency which is implicit in the diagnosis of Simmonds' disease It has been shown repeatedly that the supposedly irreversible clinical picture which frequently has led to this erroneous and hopeless diagnosis is actually completely reversible These symptoms and findings are more aptly referred to as the depressant effects of starvation and many of them are probably attributable to the depressant effects of starvation on the function of the glands of internal secretion

The results of investigative work as well as clinical observation have led us to suspect that the origin of some of the manifestations of starvation may rightfully be placed in certain of the glands of internal secretion *For example, the lowered basal metabolic rate, which serves as a mechanism of protec*tion for the starving individual, can perhaps be attributed to failure in production of the thyrotropic hormone A failure in production of the adrenocorticotropic hormone most likely is responsible for the common findings of low values for both 17 ketosteroids and cortin like substances (11-oxysteroids) in the urine, impairment of diuresis following the ingestion of large quantities of water (a similar result being observed in Addison's disease) and the frequent finding of relative lymphocytosis which likewise characterizes Addison's disease The low blood pressure, slow pulse rate, and marked weakness, the last of which is commonly seen in older individuals, and not uncommonly seen in young individuals who exhibit marked emaciation, likewise can be ascribed in part at least to a lack of adrenocorticotropic hormone The unexplained pallor which occurs without anemia and which characterizes the victim of anorexia nervosa suggests a dysfunction of the anterior lobe of the pituitary body, for similar pallor is one of the prominent recognizable findings of anterior pituitary insufficiency While the amenorrhea of anorexia nervosa has been attributed either to psychic disturbances or to the effects of starvation, its direct cause can be traced to a lack of gonadotropic hormone, for the resumption of menstruation may be foretold by the reappearance of prolan and estrin in biologic assays of the urine *The over all picture from the labora-*

tory point of view is that of severe but reversible anterior pituitary insufficiency It is the recognition of this reversibility which has given to this clinical entity a hopeful rather than a hopeless prognosis

Treatment The attitude of the physician and his ability to obtain and hold the confidence of the patient is the secret of successful treatment The actual treatment of the manition itself is a simple problem of dietetics

THE APPROACH *Consideration Given Emotional and Psychic Disturbances* The physician must remember at all times that he is dealing with an individual who is psychically and emotionally disturbed He also should keep in mind that many of these patients are well above the average in intelligence In many cases the attitude of the patient s family toward her * illness previous unsuccessful attempts at treatment and previous erroneous diagnoses have produced a skepticism toward all therapeutic suggestions Because of these mental peculiarities no fanciful explanations should be attempted and the discussion should be sincere straightforward and impersonal It is of equal importance that the patient not be antagonized while receiving a minimal amount of sympathy In this manner the physician seeks willing co operation and once the patient s confidence is obtained the physician may be surprised by the degree of enthusiastic co operation Such an attitude toward the patient has the tendency to dis [illegible] ges and to prevent manifes [illegible] should [illegible] ve that it is important that the treatment of each individual patient and the consultations with her be limited to the supervision of one physician

It is advisable to reserve psychiatric studies or a discussion of the psychic and emotional disturbances until the patient has recovered from the debilitating effects of the illness Premature efforts to probe the peculiarities of the personality of the patient often induce an antagonistic attitude which renders somatic therapy difficult Adequate time for obtaining information concerning the psychic disturbance is afforded during treatment and suggestions for correction of causative situations may be given when recovery is well under way Subsequent pointed psychiatric examinations are unnecessary except for academic interest

Preliminary Discussion The preliminary discussion with the patient and her relatives is of great importance as without this complete co operation can hardly be expected The dietetic basis for her manition an outline of the treatment to be carried out and the reason the treatment is to be carried out in the manner to be described should be explained to the patient in detail before treatment is begun Sufficient time should be given to this discussion in order that the patient may understand the problem and what is expected of her It is important to discuss the patient s symptoms with her and to explain to her that these symptoms have been the result of the starvation which she has undergone It should be pointed out that the distress and the feeling of fullness and distention after meals have resulted from the progressively lessened amount of bulk in her diet over a period of time and that in this manner she had trained herself to become intolerant to more than a small amount of food at any one time

It should be explained that the treatment is aimed at the reverse procedure that by progressively increasing the amount of bulk in her diet at mealtime she will gradually become accustomed to this increase and that a point will be reached at which the postprandial distress will gradually lessen and disappear The patient should be reassured that in spite of her aversion to food and her postprandial symptoms the treatment will cause her no great discomfort and that her aversion to food will decrease as a part of her recovery It should be pointed out however that she should expect some increase in the postprandial distress during the first few increases in the diet but that it is necessary that she tolerate this before her symptoms become less She should be assured that by putting up with this preliminary distress she will reach a point at which the caloric value of the diet will allow her to overcome her manition

If vomiting has been present it should be

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* Anorexia nervosa occurs in the male but with such comparative infrequency that for reasons of facility in presentation no reference is made to males

explained much in the same manner and on the basis of its being a conditioned reflex The active stimulus for this reflex is a sense of fullness which with the passage of time has occurred at a lower and lower threshold and has appeared when less and less bulk has been present in the stomach No increase in the bulk of the diet which should be initially small should be attempted until vomiting has been overcome

Roentgenoscopic studies of the stomach are prerequisites to treatment if for no other reason than to reassure the patient that no obstruction exists at the outlet She also should be reassured that the stomach was found to be of normal volume as these patients not infrequently will make the statement that their stomachs have shrunk"

The patient should be told that usually the time required to increase her diet to the required amount will be approximately 6 weeks one week being necessary for each *increase of 300 calories It should be empha*sized however that the primary interest in this 6 weeks of treatment is not in the amount of weight gained in that time but in the fact that at the end of that period she will

so that on the nd the ive re turned to her standard weight and will have been relieved of the symptoms caused by her inanition In the event of co operation a promise of complete recovery from all symptoms and changes secondary to starvation can be given with impunity with the one exception of amenorrhea The latter is dependent on the degree and duration of the starvation and its duration should not be predicted

Dietary Treatment The series of events which accompany gradual decreases or increases in the bulk of the diet is entirely sub*jective and must be listed under the heading* of psychosomatic phenomena A situation analogous to this variability of the "comfort capacity" of the stomach is seen in the physiologic similarity manifested in the urinary bladder during the development of as well as during the recovery from the condition known as "habit frequency"

Sudden increases in the bulk of the diet such as starting patients who have been taking 1 300 calories or less on a diet with a value of 3 000 calories are followed by upper abdominal distress lack of confidence and co operation and consequently failure however small increases in the bulk of the diet may be made at regular intervals without causing the patient sufficient discomfort to

theless increasing a high protein diet by 300 calories at a time will gradually increase the bulk of the diet A rough estimate of the patient s daily caloric intake prior to admission is made and to this amount are added 300 calories The patient is given a high protein high vitamin diet based on that number of calories (1300 to 1600 calories or less) and is asked to eat everything served her *For the first few days she may complain* of distress and a sensation of fullness however after several days these symptoms begin to lessen After 5 or 6 days the caloric content of the diet may be increased by another 300 calories For the next 2 or 3 days discomfort after meals may be experienced again however the symptoms again gradually become less This procedure is repeated until the daily intake reaches 3200 calories These patients experience far less distress from eating this amount than they had experienced after the meals of the initial diet which was based on 1300 calories or less

The food values of the diets as used in caloric increases are given in Table I

TABLE I

Food Values in Diets

Carbohydrates gm	*Protein gm*	*Fat gm*	*Calories*
115	71	60	1 300
150	73	79	1 600
187	75	93	1 900
219	80	114	2,200
245	83	135	2,500
295	91	185	3,200

The increase from 2500 to 3200 calories may be made by rearrangement of foods in

the diet without much increase in the bulk A diet of 3200 calories is unquestionably ample enough to permit gain in weight in all instances In some instances dietetic instructions in a high protein high vitamin diet with instructions to begin with a diet valued at 1300 calories and to increase the diet each week by an addition of 300 calories until a diet containing 3200 calories has been reached has proved successful when carried out in the patient s home

In most cases it is important for the physician to see the patient every day until she has developed enough confidence to overcome the aversion to food which previously had been the dominating factor militating against her recovery

When cachexia is extreme treatment must be cautious and undertaken with the understanding that little or no improvement can be expected for some time Aggressive treatment of patients who have extreme degrees of emaciation may prove disastrous The necessity for tube feeding or for daily intravenous administration of fluid is a sign of danger and in such cases treatment should proceed with caution

Management of Accompanying Conditions and Supportive Measures The finding of a relative degree of lymphocytosis is common in cases of anorexia nervosa and should cause no concern It may be related to depressed function of the adrenal cortex The return to normal may occur early during treatment Likewise leukopenia is a common finding and the leukocytes in certain instances may be found sufficiently low in number to cause concern This finding also has been found not to be of significance and the return to normal occurs later during recovery

Anemia is not an uncommon finding and in rare instances may be severe During treatment of the anorexia the anemia may be found to increase or appear for the first time secondary to retention of fluid as a consequence of treatment The administration of 0 3 gm of ferrous sulfate after each meal is indicated when anemia is found Transfusions are rarely indicated and only when the anemia is severe

Pitting edema of the ankles or in some instances generalized edema may occur concomitantly with a gain in weight of as much as 15 lbs (6 8 kg) during the first 2 weeks of treatment Both of these are due to a retention of fluid as a result of a successful increase in the diet and do not signify cardiac or renal failure The edema may persist for from several weeks to 2 months or longer After the original gain in weight there may be no gain for several weeks or longer however observation of the patient will show unquestioned and progressive improvement The weight curve may be misleading if used as a basis for the actual storage of flesh With the gradual disappearance of edema the weight of water lost may be approximately equal to the weight of the flesh gained At the end of the period during which water is lost the patient will show a progressive gain in weight

During the first few weeks 30 mg of phenobarbital given two or three times a day and 10 drops of tincture of belladonna in ½ glass of water 20 minutes before meals

patient

in the

excretory

urogram as renal calculi have been found in a number of instances These patients drink very little fluid and as a result the urinary output is markedly decreased Some of them probably because of a negative nitrogen balance have a tendency to osteoporosis and consequently excrete excessive amounts of calcium in the urine All of these factors favor the formation of stones in the urinary tract

Patients should be warned against falling Osteoporosis in some instances may be marked I have seen several severe fractures occurring in these patients as the result of a minor fall during treatment

As a rule to patients who are seen after many months of inanition associated with amenorrhea estrogens may be administered cyclically 3 weeks out of 4 Doses of 0 5 mg of diethylstilbestrol daily by mouth may be used This is done to aid in priming the uterus for subsequent return to ovarian function and to shorten the period of marked atrophy often seen in these cases Usually approximately 6 months is required for these patients to regain their standard weights however in some instances the return of the normal menstrual cycle may require a much longer period

It is surprising that these patients are exceptionally free from infections that terminate chronic debilitating diseases In fact it is unusual to find them suffering from any complicating disease

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NUTRITIONAL EDEMA

Nutritional edema (famine edema) can no longer be considered as a simple manifestation of protein deficiency instead it is to be

plasma protein this is not an invariable rule and even when hypoproteinemia is present the decrease may be but slight Renal or cardiac failure is not a necessary part of the picture of famine edema

The treatment of famine edema is essentially the treatment of semistarvation Absolute bed rest is essential for the very ill with restricted ambulation for the less severely ill Orally administered nutrients are preferable to parenteral alimentation It is important not to overfeed patients during the first few days of re-alimentation More than small amounts of fat are not well tolerated in the initial diet

One of the most valuable therapeutic agents for initial refeeding of severely starved patients is dried skim milk The experience during World War II provided no basis for belief that protein hydrolysates administered parenterally to individuals with nutritional edema is not to be recommended as there is danger of producing circulatory failure by the sudden administration of large quantities of parenteral fluid These patients will usually tolerate reasonable quantities of protein orally If however the serum protein levels are considerably reduced the cautious administration of salt free human plasma albumin serves to increase the serum protein concentration and usually results in a diuresis with resultant loss of tissue fluid

The moderately and less severely ill cases of nutritional edema are best treated by a diet low in fat and composed of simple foods high in protein of good biologic value Such foods are milk eggs and meat In addition the diet should contain cereals and fresh fruit Initially the daily diet should contain 200 or 300 calories more than the intake level of the patient for the period immediately preceding therapy The quantity of diet should be gradually increased by increments of 100 to 300 calories each 1 to 3 days as tolerated by the patient It is essential to adjust the diet of the patient to his tolerance Even in severe cases within 2 to 4 weeks after the institution of therapy the patient can usually tolerate 3000 to 4000 calories without gastric discomfort or vomiting

Inasmuch as these patients seldom present evidence of specific nutritional deficiencies other than calories and protein it is usually unnecessary to administer supplementary vitamins In occasional instances however pigmentation of the skin and glossitis may be relieved by the addition of supplementary niacin in moderate doses of 50 to 100 mg per day The moderate anemia which frequently accompanies starvation does not respond to liver extract or iron Mercurial diuretics or digitalis are not needed unless cardiac failure exists

The general care of such patients includes the control of intercurrent infection with sulfonamides or antibiotics protection from cold and chilling to which such patients are particularly sensitive and sympathetic nursing

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CHAPTER VI

DISEASES OF THE DIGESTIVE TRACT

DISEASES OF THE MOUTH, ESOPHAGUS, AND STOMACH

VINCENT S ANGINA

(Trench Mouth Fusospirillosis Ulceromembranous Stomatitis)

This mildly contagious disease of the mucosa is usually confined to the tonsils, but sometimes affects the pharynx, mouth, gums, and even the larynx and trachea During World War II a large number of cases were seen and gave ample opportunity for the use of the newer antibiotics Comparison with the older drugs showed that arsenic in its various forms, chromic acid, gentian violet, and other such drugs in popular usage are definitely less effective than penicillin or the sulfonamides

Penicillin Penicillin produces a quick response and symptomatic cure It may be used locally in the form of pastilles or lozenges, each containing 5000 units of penicillin, or it may be administered parenterally In treating over 400 cases in the Navy, Strong and Willett sprayed the mouth with penicillin solution (250 units per cubic centimeter) and then prescribed penicillin lozenges to be dissolved in the mouth at hourly intervals This procedure was carried out daily for 2 or more days It was found that smears became negative in from 48 to 120 hours, while symptoms were relieved in 24 hours

In severe cases the parenteral use of penicillin is preferred, 20,000 units being given every 3 hours to a total of 100,000 units In patients not hospitalized, long-acting penicillin in a dosage of 300,000 units daily for 3 days may be used

Sulfonamides In 1945 Manson and Craig treated 48 cases of Vincent's angina with 0 5 gm sulfathiazole tablets orally The symptoms disappeared in 24 hours, but they continued treatment for another 72 hours In Wolfram's series of 61 Army Air Corps cases, 41 were treated with sulfadiazine or sulfathiazole, the daily dose being 6 gm, and the total dose per patient being 12 to 38 gm In 78 per cent of these patients, the lesions healed in less than 20 days, but in the control series, treated with chromic acid, gentian violet, neoarsphenamine, or mapharsen, and locally with glycerine or with vitamin supplements, only 25 per cent of the patients had their lesions healed in less than 20 days

Other Drugs W M Johnson used nicotinic acid (niacin) systemically, and found that his patients were relieved of symptoms in about a week To adults he gave 50 mg three times daily, and to children 10 to 50 mg three times daily, depending on the age of the child

In the routine treatment of soldiers suffering from Vincent's angina, Kent advised the use of ascorbic acid (vitamin C) and recommended 0 6 gm daily for the first week, and 0 3 gm daily thereafter

Local treatment to rid the mouth of the necrotic membrane consists of the use of hydrogen peroxide as a mouth wash This should be done every 3 or 4 hours, the disinfectant being used in full strength or diluted one half Relief is also given by sodium perborate used as a paste with cotton applicators or as a mouth wash

Oral hygiene and prophylaxis and the removal of calculi and peridontal pockets are of the greatest importance in both acute and chronic cases

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STOMATITIS

Knowledge of the causes of inflammation of the oral mucous membrane stomatitis has advanced so much in recent years that treatment now follows etiologic lines rather than those based on an outdated descriptive classification The physiologic and pathologic state of this membrane depends either on local insult or on response to some systemic pathologic agent or disease Local trauma includes reactions to heat and to chemicals as well as the closely related reactions to bacterial and mycotic infections and to viruses Systemic diseases producing oral lesions include the blood diseases such as agranulocytic angina leukemia purpura and pernicious anemia the deficiency diseases such as sprue beriberi and pellagra and those conditions characterized by severe diarrhea Many of these diseases will be discussed elsewhere only a few being considered here

[illegible]

[illegible] and Mikulicz s (periadenitis mucosa necrotica recurrens) should be grouped together since they all respond equally well to the same treatment

Van Rooyen and Rhodes report that vesicle fluid from all varieties of herpetic eruptions can be inoculated into human skin with consequent production of a typical crop of simplex vesicles and that when the antibody content of serum of individuals subject to [illegible]

[illegible] This can be accomplished by using the patient s own vesicular fluid or as suggested by Foster and Abshier by repeated vaccination Woodburne advocates repeated vaccination with smallpox vaccine at 1 to 2 week intervals unless a "take" occurs in which case the reaction is allowed to subside before further vaccination

Local treatment consists in the use of mouth washes of dilute sodium perborate or hydrogen peroxide In infants the mouth may be cleansed with these solutions In chronic recurrent herpetic stomatitis a silver nitrate stick applied to the base of the ulcer has been used effectively

Gangrenous Stomatitis (Noma Cancrum Oris) Most authors are of the opinion that there is no specific treatment for gangrenous stomatitis (Wang Sung and Sung) but that early diagnosis and prompt measures to improve the nutritional state of the patient are essential Agnew advises the use of massive multivitamin therapy especially vitamins A B complex, C and D and in addition a high caloric high protein and high vitamin diet.

Wang Sung and Sung advise against surgical excision but they do advise removal of necrotic tissue irrigation of the mouth with 1 1000 potassium permanganate solution twice daily and a warm saline solution rinse every 30 minutes In addition blood transfusions are given to patients seriously ill Agnew believes in excision into healthy tissue by electrocautery

Favorable results have followed the use of a 1 to 4 day treatment with sulfathiazole or sulfadiazine in single doses of from 0 9 gm to 4 00 gm with a total dosage of from 4 5 gm to 18 gm daily

Dawson combines the use of penicillin [illegible]

Stomatitis Following the Use of Penicillin Streptomycin and the Sulfonamides Since the advent of these drugs stomatitis has been seen in association with their administration It has been noted that penicillin administered orally has been more prone to produce stomatitis than that given parenterally, and it is the general opinion that the parenteral use in itself does not produce oral lesions Ellinger and Shattock have noted that penicillin treated patients may develop a stomatitis involving the entire mouth—tongue cheeks and palate—with the mucous membrane becoming red tender and edematous In such patients they were able to demonstrate a nicotinamide deficiency, the degree depending upon the relative effect on intestinal flora Daily urinary nicotina

mide was determined before during and after oral administration of penicillin Oral lesions appeared within 3 to 4 days following therapy and after the sixth day the patient became forgetful and experienced difficulty in maintaining equilibrium These authors also noted similar symptoms in some patients after sulfadiazine therapy They advise the use of nicotinic acid 100 mg daily given either orally or parenterally to any individual maintained on oral penicillin

Phillips reports 5 patients receiving oral penicillin who after 24 hours developed a burning sensation in the mouth and throat and a soreness of the gums together with aphthous like lesions which ulcerated leaving a dirty gray base The tongue became beefy red and painful

The author has seen painful stomatitis with a beefy red tongue and red buccal mucous membrane following the use of penicillin orally by inhalation

Beham and Perr report the occurrence of painful stomatitis of the aphthous variety developing during streptomycin treatment of both pulmonary and extrapulmonary tuberculosis The lesion healed rapidly with discontinuance of the streptomycin only to reappear with resumption of the drug He was unable to correlate the stomatitis with the daily or with the total amount given or with the duration of administration

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ESOPHAGITIS

Esophagitis is probably the most common disease of the esophagus since it occurs in a large number of conditions Because of its anatomic structure the esophagus is unusually vulnerable to pathogenic organisms from the oral cavity from regurgitated stomach contents and from intra abdominal infections passing through the blood stream and lymph channels

Treatment should be directed toward the fundamental causes which can be classified as follows (1) traumatic as after the frequent passage of stomach tubes after repeated vomiting after the drinking of escharotics strong acids alkalies and other poisons and after the swallowing of foreign bodies (2) in association with severe infections and debilitating diseases (3) in connection with abdominal diseases such as cholecystitis duodenal ulcer and appendicitis (4) in relation to certain abnormalities of the esophagus itself such as hiatal hernia esophageal diverticula cardiospasm and esophageal varices Other diseases such as thrush syphilis tuberculosis and actinomycosis will be considered elsewhere

In group 1 the simplest form of management is prevention i e care in the passage of stomach tubes control of vomiting and prevention of the accidental swallowing of poisons and foreign bodies But once acute esophagitis is established treatment is directed first to relief of pain by such measures as the application of an ice bag to the sternum and neck and the swallowing of ice in small bits held in the mouth Tincture of belladonna 20 drops every 4 hours will relieve spasm The diet is bland and the belladonna can be given 20 minutes before each feeding Bastedo advises the use of an unsweetened lozenge containing 2 grains (0 13 gm) of ethyl aminobenzoate dissolved in the mouth to produce an anesthetic effect and to allay pain and spasm when food is swallowed Small amounts of olive oil or milk every 3 to 4 hours give relief

In esophagitis due to chemical trauma the same regimen can be followed but the esophagus should be put at rest by feeding

the patient with a duodenal tube kept in situ In addition sedatives such as phenobarbital 30 mg three times daily should be used if the pain is severe and intravenous 5 per cent glucose should be administered as sup portive treatment if there is definite dehy dration

In cases where the condition does not improve or where the acute condition has subsided particularly after the swallowing of chemicals it is well to study the esopha gus roentgenologically in order to determine the amount of stenosis In early cases it may be necessary to perform gastrostomy until the acute or subacute stage has subsided and scar tissue has formed After stricture forms in cases following the drinking of es charotics graduated bougies should be passed after the patient has swallowed a guiding thread In those cases too where there persists a good deal of esophageal spasm the passing of graduated bougies frequently gives relief This can be said also of cases where ulcer forms Barclay recom mends the passage of bougies to stretch the base of the ulcer and finds that relief of symptoms and actual healing may follow such a procedure

In group 2 treatment is naturally directed toward the underlying pathology Esopha gitis is frequently associated with debilitat ing conditions such as severe burns diabetes mellitus typhoid fever arteriosclerosis etc

In group 3 treatment is likewise directed toward the intra abdominal disease and the primary lesion—cholecystitis duodenal ulcer or appendicitis—must be considered

In group 4 where abnormalities of the esophagus precipitate the esophagitis cer tain conditions should be evaluated such as regurgitation of acid stomach contents in hiatal hernia cardiospasm or the ulceration associated with esophageal varices in hepatic cirrhosis The treatment of these conditions will be considered elsewhere

ARTHUR E MAHLE

PEPTIC ULCER OF THE ESOPHAGUS

Peptic ulcer of the esophagus as a primary entity is rare although esophagitis and peptic ulcer of the esophagus in association with certain anomalies are not too uncom mon In hiatal hernia particularly with a congenitally short esophagus the occurrence of an ulcer between the esophageal and the gastric mucosa is not infrequent In addition many patients give a history of previous gas tric or duodenal ulcer or of cholecystitis In such cases hematemesis may occur and may be severe

Treatment in the early stages attempts to rest the esophagus and to prevent regurgi tation of the acid stomach contents The diet is that used in peptic ulcer except that the feedings may be larger and less frequent One follows the usual Sippy treatment be ginning with liquids and later adding more solid foods to the diet but keeping it bland Alkalis and antacids such as aluminum hy droxide gel are given between feedings and some advise the use of olive oil or the suck ing of bismuth lozenges Belladonna 20 drops of the tincture or atropine 1/100 grain (0 6 mg) by hypodermic may relieve spasm

If the dysphagia persists and is marked and if on fluoroscopic examination with barium the esophagus shows considerable spasm dilatation with graduated bougies may give relief Gastrostomy or jejunostomy has been performed in some intractable cases

In a case reported by Morton and Brun schwig observed over a 10 year period gastrostomy was performed because of com [illegible]

a duodenal ulcer was found but no change in the roentgenologic picture was noted

Ruptures of a peptic ulcer of the esopha gus have not infrequently been reported with a resulting high mortality Preiskel reports such a case with rupture into the mediasti num but with recovery

In summary peptic ulcer of the esopha gus should be treated medically by diet antacids antispasmodics and rest If this regimen gives no relief and if dysphagia and spasm of the lower esophagus are demon [illegible]

with the aid of a previously swallowed guide thread Satisfactory results are obtained with bougies graduated from No 27 to No 45 French Gastrostomy and jejunostomy are rarely necessary

ARTHUR E. MAHLE

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FUNCTIONAL INDIGESTION

CARDIOSPASM

Cardiospasm may be mild, when the symptoms are chiefly pain, moderate dysphagia, and regurgitation or more advanced, with marked dysphagia, regurgitation, vomiting and pain the latter rather moderate in severity In the milder cases there is but little weight loss and nutrition is only slightly impaired, but in the severe cases the weight loss is marked there is emaciation with dehydration and the symptoms are of long duration On ingestion of barium these patients are found to have a smooth obstruction at the cardia, moderate to marked dilatation of the esophagus above the obstruction, and frequently a marked tortuosity of the esophagus

Treatment of cardiospasm is threefold (1) medical, (2) mechanical (dilatation of the esophagus) (3) operative (Vinson)

Medical Therapy The drugs used in treatment are those employed to relieve spasm of the cardia of the esophagus Vinson found that the use of tincture of belladonna in doses of 20 drops brought only temporary relief This is also true of hypodermic injections of atropine 0 4 mg to 0 6 mg, and after long usage the drug may have to be increased to as much as 15 mg before eating Robinson and Wilkinson were able to relieve cardiospasm at first with the use of octyl nitrite (the nitroso ester of 2 ethyl n hexyl nitrite) in 3 minim ampules, broken in a handkerchief and inhaled As tolerance to the drug developed, its effectiveness was lost To date, drug therapy has failed to relieve true cardiospasm with any degree of permanency, and this failure has resulted in the employment of mechanical and operative measures to relieve symptoms

Mechanical Therapy The great majority of patients suffering from cardiospasm can be treated successfully by dilatation Peterson states that in 95 per cent of cases the disease can be cured by hydrostatic dilatation Clagett and his co workers state that 70 per cent of patients with cardiospasm can be completely relieved by one course of treatment with the hydrostatic dilator In 30 per cent there is a tendency to recurrence which may take place at any time, immediately after treatment or as long as 25 years later When there is recurrence the majority of patients can be relieved by subsequent dilatation In approximately 2 to 5 per cent of patients dilatation has not proved efficacious, and here surgical intervention is indicated

The method of dilating the cardia by hydrostatic pressure, as used by Vinson Moersch, and others was devised by Russell and improved by Plummer This method is ably described by Vinson The patient is instructed to swallow a silk twist thread usually about 5 yards long until the thread engages itself firmly in the loops of the intestines and is thus anchored The thread can be started the evening before the contemplated dilatation, the patient being directed to swallow about 1 ft an hour

The dilatation procedure is as follows A No 45 French olive is threaded upon the silk thread and guided down the esophagus This is followed at once by a No 60 French olive, likewise passed through the cardia Many patients with mild cardiospasm will gain relief from this procedure alone or will gain temporary relief for some months, after which repetition of the passage of the sound may be done This is particularly advisable in elderly patients

If relief is not obtained by passage of a No 60 French bougie or if the dilatation is so marked that it is obvious that such a procedure may not be of benefit, the hydro-

static bag is then introduced This procedure is usually carried out about a week after the passage of the No 60 French olive The hydrostatic bag is introduced over the thread into the cardia to the most dependent portion of the esophagus Then the thread is pulled taut and the dilator advanced to the correct depth so that the center of the dilator lies in the cardia It is then held in place and distended with water until the gauge registers a pressure of 22 to 24 ft of water If the dilator has properly engaged the constriction at the cardia the patient will experience severe pain as the dilator expands Occasionally the dilator slips out of the narrowed cardia usually into the stomach but after a small amount of water is released the bag can again be pulled into the cardia and the dilatation resumed This procedure as carried out by Vinson is done without anesthesia or the use of fluoroscopy for he feels that the handicap of attempting dilatation in the dark is greater than the advantage gained by visualizing the dilator in the cardia

Complications of this procedure as in any type of instrumentation of the esophagus include perforation with resulting mediastinitis usually fatal However since 1925 Vinson has had no fatal outcome in the more than 450 patients upon whom he has performed hydrostatic dilatation and he is of the opinion that the preliminary passage of the No 60 French olive prevents over distention if the hydrostatic bag alone is used in the preliminary dilatation

In some methods for dilating the cardia air is used instead of water Such an apparatus has been devised by Sippy Einhorn and others The dilating bag is passed in the usual manner and inflated by means of a sphygmomanometer bulb to the necessary pressure and diameter

In 1913 and 1929 Hurst devised rubber tubes of –

ospasm

31/16 to 4?

31 in in length each containing the same weight of mercury (1 lb 5 oz) In 1929 Hurst described his technic for the passage of such mercury bougies and advised that it was best to pass such a bougie during the roentgen examination and to mark the bougie at the level of the incisor teeth with the lower end extended 2 in within the stomach Successively larger bougies are passed the patients being taught to pass

after a week or if relief is not yet attained the bougie can be passed at intervals of every other day to a week On several occasions the author has used a No 60 French mercury bougie for mild cardiospasm in place of the No 60 French bougie and secured relief in selected cases In advanced cardiospasm Hurst advises the use of the Plummer hydrostatic bag because the mercury tube will curl up in the lower esophagus and not pass through the cardia into the stomach

Operative Treatment Of the operative measures used simple gastrostomy alone is the procedure of choice and by this means the patient is fed with a gastrostomy tube This does not relieve the primary obstruction although it may save the patient s life When it has served its purpose other means of relieving the cardia obstruction should be employed

When the stomach has to be opened for the purpose of feeding Vinson advises the manual dilatation of the cardia through the gastrostomy and finds that a previously swallowed thread is helpful in locating the cardiac opening In 2 of his cases where angulation of the esophagus prevented introduction of a dilator into the cardia this type of manual dilatation was quite satisfactory

Sympathectomy operations on the cardiac sphincter removal of abdominal sympathetic ganglia and removal of the cervical sympathetic ganglia have all been performed with but little benefit

Recently there have been reports of intractable cardiospasm treated successfully by esophagogastrostomy Clagett Moersch and Fischer reported 4 patients successfully so treated Good functional results were obtained but the dilated esophagus did not appear to reduce appreciably in size following the operation In reviewing the literature these authors came to the conclusion that the transperitoneal route carried a lower operative mortality than the transpleural route The 4 cases reported were patients with long standing cardiospasm in whom

dilatation of the cardia had failed to produce more than temporary relief

Peterson reports 10 cases operated upon for marked cardiospasm esophagogastrostomy being performed in 9 by the transpleural route and in one by the abdominal route He is of the opinion that the procedure is a safe one and is a means of providing relief of symptoms in cardiospasm

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PYLOROSPASM

As the term signifies pylorospasm is defined as spasm of the pyloric muscle In infants it is closely related to pyloric stenosis and *must be considered in the differential* [illegible]

[illegible] larly with hypertrophic antral gastritis In pylorospasm from extragastric lesions one must consider cholecystitis appendicitis *pancreatitis and* diseases of the urinary tract The condition also occurs in certain neurogenic and psychoneurotic states among which are included migraine anorexia nervosa and other emotional states The projectile vomiting related to intracranial pressure from brain tumor can be considered a reflex pylorospasm

Treatment should be directed to the underlying disease for in adults pylorospasm is merely a symptom in differential diagnosis and not a disease *in itself*

In peptic ulcer the therapy is obvious and where there is pylorospasm without sign of gastric retention medical management of the ulcer should be instituted But in hypertrophic antral gastritis surgical treatment should not be delayed in those doubtful cases where differentiation from cancer is difficult Despite the combined clinical roentgenologic and gastroscopic examination of such patients there is error of diagnosis *in about 20 per cent of cases*

In the second group that of cases related to functional and to extragastric organic disease—to brain tumor cholecystitis and emotional states—therapy should be directed toward appreciation of the basic disturbance

During the time the patient is undergoing various *examinations to determine the cause* of the pylorospasm symptomatic therapy is indicated The use of a bland diet with 10 drops of tincture of belladonna and 30 mg of phenobarbital before each meal often provides temporary relief of discomfort

ARTHUR E MAHLE

HYPERCHLORHYDRIA AND HYPOCHLORHYDRIA

Any discussion of the therapy of hyperchlorhydria or hypochlorhydria immediately introduces the question of what constitutes normal gastric acidity and what if any symptoms an abnormal acidity can be *expected to produce* A great deal of experimental work has been done on the relationship of gastric acidity to the total gastric secretion and on the importance *of the secretion* of mucus pepsin etc Next to be evaluated is the influence of intrinsic and extrinsic factors on gastric secretion from [illegible] and [illegible] ffect [illegible] the [illegible]

effect of certain drugs and chemicals the *stimulating effect of histamine* the inhibiting action of urogastrone the neutralizing action of the antacids and the buffer action of milk and cream on *neutralization—all must* be considered

Hyperchlorhydria Some patients with excessive acidity get relief from the use of antacids such as aluminum hydroxide preparations but the interesting point is that

many of these patients seem to experience relief merely because of the eructation of the gas which so frequently follows the taking of antacids Two ounces each of milk and cream will frequently relieve the symptoms of excessive acid secretion

[illegible] evidence [illegible] is low [illegible] show no symptoms of intestinal disturbance any *more than do those whose acidity is ab* normally high

It is perfectly simple to augment gastric secretion with hydrochloric acid and it is generally accepted that some older patients with hypochlorhydria have vague gastro intestinal symptoms even disturbing diar rhea which are relieved with the ingestion of 4 cc of dilute hydrochloric acid with meals The acid should be taken through a *glass drinking tube to avoid injury to the* enamel of the teeth A proprietary prepara tion called acidulin may be taken in tablet form 1 tablet with each meal in place of the liquid hydrochloric acid

In summary hyperchlorhydria and hypo chlorhydria are in themselves not impor tant causes of symptoms but result from many factors both intrinsic and extrinsic and should so be considered and treated

ARTHUR E MAHLE

GASTRITIS

Acute Gastritis Acute inflammation of the stomach may be provoked by abuse and injury from irritating food or drink such as strong spices alcohol coarse fibers seeds or skins from corrosive chemicals or drugs or from hematogenic invasion by bacteria Depending on the kind and source of the insult the inflammatory reaction may be hyperemia congestion edema hemorrhage erosive ulceration suppuration or abscess

ACUTE SIMPLE EXOGENOUS GASTRITIS This condition is caused by overindulgence in quantity or to poor quality of food or liquid and consequent irritation of the gastric mu cosa The condition is commonly self treated and transient Physical discomfort comprises nausea vomiting anorexia and abdominal distress Occasionally the lower intestinal tract may be affected with resultant crampy diarrhea When symptoms do not subside promptly with home remedies, medical at tention is sought

If nausea and vomiting persist the stom [illegible]

liquids often subdue the nausea Absorbent substances such as dry salted toast puffed rice or salted soda crackers may be more acceptable than liquids Citrate of magnesia may be advisable to clear the bowel or a warm enema to quiet the colon Effervescent bromide mixture gives helpful sedation Generally opiates are not well tolerated but 30 mg of codeine and 0 4 mg of atropine may be given hypodermically if required After fasting for 24 to 48 hours warm liquids are taken Soft and then semisolid foods are added gradually until the resumption of the usual diet within 4 or 5 days

ACUTE CORROSIVE GASTRITIS *This form of* gastritis results from deliberate or accidental swallowing of poison strong chemical solu tion or excessive amount of a drug Gastric symptoms are apt to be more severe than those of simple gastritis and may include systemic signs according to the nature and action of the substance ingested Stomach washing is usually necessary The following solutions are suggested for lavage of the *stomach*

For Strong Acids Large quantities of fluids for dilution solutions may contain 2 oz of milk of magnesia or 8 gm of soda bicarbonate or plain soap suds

For Oxalic Acid Solutions of calcium and magnesium bases

For Alkalis Weak acids lemon juice di lute vinegar

For Phenol Sodium sulfate 15 gm in 500 cc water

For Iodine Starch solution

For Mercury Wash the stomach with water then egg and milk prime considera tion is prevention of renal damage

For Silver Nitrate Plain table salt

For Zinc Salts Sodium or potassium car bonate

[illegible]

oz. ferric chloride and ½ oz. sodium carbonate in a glass of water Saline or castor oil purge is advisable

For Tartar Emetic Alkali strong tea or tannic acid solutions

For Lead Sulfates of magnesium and sodium

For Copper Salts Potassium ferrocyanide 1 teaspoonful in a glass of water

When systemic effects are anticipated saline or castor oil catharsis is indicated Subsequent treatment of the gastritis is that described for exogenous gastritis

Acute Hematogenous Gastritis Infectious diseases such as diphtheria influenza meningitis pneumonia and others may result in acute hematogenous gastritis Measures to relieve associated gastro intestinal discomforts are ordinarily incorporated in the management of acute epidemic and infectious diseases If the febrile illness is protracted vitamins and minerals should be supplemented to prevent development of simple inflammation into a chronic deficiency or degenerative form of gastritis

Acute Phlegmonous Gastritis Suppuration of the stomach wall may result from trauma malignant or ulcerous gastric abscess or staphylococcal streptococcal pneumococcal or *E coli* or typhosis bacteremia Treatment of the primary disease may suffice for the gastric condition but full use of sulfonamides and penicillin as indicated should be assured Gastric resection may be required

Chronic Gastritis Chronic gastritis has been accepted as an inflammatory or degenerative disease of the stomach on the basis of related roentgenographic gastroscopic and histologic demonstrations of changes in the gastric mucosa and wall Causes for acute gastritis are usually apparent etiology of chronic gastritis is except in a few instances unknown

Inherent capability of an objectively abnormal gastric mucosa to evoke subjective symptoms is questionable The lining of the stomach may appear normal atrophic or hypertrophic with no declared gastric distress Headache backache weakness fatigue insomnia anorexia and similar psychosomatic complaints may not invariably be attributed to the stomach When the gastric mucosa in any state normal atrophic or hypertrophic becomes hyperemic congested edematous eroded or ulcerated uncomfortable or painful sensations may be aroused A normal stomach is sensitive onl to stress and tension of the entire wall Presumptively, subjective symptoms arise when tissues of the mucosa submucosa muscle layer or serosa are disordered and responses to stimuli of contraction or stretching are enhanced Aberrations of secretion seldom provoke notable sensations Treatment of chronic gastritis is based on these considerations and for practical purposes may be discussed as recurrent superficial gastritis atrophic gastritis hypertrophic gastritis and gastritis of the postoperative stomach

Recurrent or Chronic Superficial Catarrhal Gastritis This form of gastritis may eventuate in atrophy of the gastric mucosa The condition occurs in stomachs that are apparently susceptible to slight insults The gastric mucosa is hyperemic congested edematous hemorrhagic often with aphthae or superficial erosions and mucopurulent exudate The symptoms are epigastric pressure distress after eating nausea and anorexia

A therapeutic regimen comprises rest construed as relief from duties and physical activities liquid semisolid or soft diet as indicated daily matinal glass of warm water

or gla

absorb

or aluminum gels 4 cc of dilute hydrochloric acid with meals when gastric secretions are anacid 30 mg of phenobarbital and 0 4 mg of atropine sulfate may be given for hypertonicity or hypersecretion Constipation should be corrected by diet and bowel training Good mastication should be assured by adequate dentures oral sepsis and sinus discharges should be eradicated When exacerbations have subsided instructions should be given to regulate eating habits to moderate use of condiments tobacco and alcohol to avoid physical fatigue or mental stress and to have proper care of febrile infectious illnesses

Atrophic Gastritis Atrophy of the gastric mucosa is readily recognized as patchy or diffuse involvement but does not always appear inflammatory That is in some instances the condition presents the aspect of primarily faulty or defective morphologic fabrication or of concurrent deficiency of elements for cell growth In other cases

evidences of quiescent or active inflammation are seen With either state, manifestations of hyperplasia and regeneration may be discernible The designation of gastritis may not be universally applicable to all gastric mucosal atrophy

Atrophy of the gastric mucosa may be associated with achlorhydria, anemia, gastric polyps, or cancer, and these ancillary disorders may be productive of the symptoms in particular cases Simple, disassociated gastric atrophy or atrophic gastritis may not incite notable subjective discomfort Consequently, therapy is frequently directed to correction of anemia by iron liver extract, folic acid or vitamins—usually B complex—as indicated, or to stopping achylic diarrhea by dilute hydrochloric acid, or to extirpation of neoplasms Dilute hydrochloric acid is used in amounts of 10 to 30 drops in a wineglass of water, to be sipped with meals For microcytic hypochromic anemia, 10 grains (0 65 gm) of ferrous sulfate are given with each meal For pernicious anemia, concentrated liver extract is injected intra

be bland and smooth without coarse or irritating food substances, and arranged as four or five daily meals The diet may be augmented by mixtures of concentrated protein, minerals and vitamins such as meretine Good dentures are essential to assure proper mastication Oral sepsis and nasopharyngeal discharges should be eradicated Alcoholic beverages are usually not well tolerated, but occasionally wine before meals will arouse the appetite

Hypertrophic Gastritis Roentgeno-

hyperactive peristalsis and pylorospasm with protrusion of redundant membrane into the base of the duodenal bulb When these phenomena are also seen through the gastroscope, with superficial erosion and ulceration, submucosal hemorrhage, edema, and exudate, the condition may be properly designated as inflammation that is, hypertrophic gastritis When the changes described are observed in the stomach, subjective symptoms may be expected Abdominal complaints in a case of indubitable hypertrophic gastritis are similar to those induced by peptic ulcer, except that epigastric distress may be felt immediately after eating, and pain experienced when the stomach is empty is not readily relieved by ingesta Nausea and vomiting are common, but nocturnal discomfort is rare The epigastric pain is diffuse and does not radiate

arranged in three approximately equal amounts of food supplemented with feedings between meals A glass of hot water with a pinch of salt, or carbonated alkaline water such as Vichy, or hot weak tea taken on arising may wash away or dilute accumulated night secretions A sedative antispasmodic mixture, such as a tablet of 30 mg (½ grain) phenobarbital with 7 5 mg (⅛ grain) extract of belladonna may be beneficial, given at 11 A M , 5 P M , and at bedtime Absorbents, as the aluminum gels, may be prescribed to be taken between meals, before or after the midday feedings, as indicated by the occurrence of pain Liquid suspensions, 1 or 2 teaspoonfuls in ½ glass of water, are better than tablets Gastric lavage with weak solutions of peroxide or silver nitrate has been recommended, but is seldom necessary Deep roentgen therapy has been used in severe and intractable hypertrophic gastritis, but is not advisable for the ordinary case, consequent atrophy and vascular damage may be more harmful than the mucosal hypertrophy

Gastritis of the Postoperative Stomach The gastric mucosa of a whole or resected stomach with a jejunostomy, is invariably inflamed Congestion, hyperemia, edema, hemorrhage, erosion, ulceration, hypertrophy, and atrophy may exist in variable degrees Slight alterations evoke no uncomfortable sensations Symptoms due to immediate postprandial hyperglycemia or from late hypoglycemia may be abolished by adjustment of the food intake to frequent equal meals, balanced with respect to protein and carbohydrate

For Tartar Emetic Alkali, strong tea, or tannic acid solutions

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t [illegible]

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A therapeutic regimen comprises rest construed as relief from duties and physical activities liquid, semisolid or soft diet as indicated daily matinal glass of warm water with pinch of salt or soda bicarbonate or glass of alkaline water such as Vichy absorbents between meals, such as kaolin or aluminum gels, 4 cc of dilute hydrochloric acid with meals when gastric secretions are anacid, 30 mg of phenobarbital

bowel training Good mastication should be assured by adequate dentures, oral sepsis and sinus discharges should be eradicated When exacerbations have subsided, instructions should be given to regulate eating habits, to moderate use of condiments, tobacco, and alcohol, to avoid physical fatigue or mental stress, and to have proper care of febrile, infectious illnesses

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hemoglobin values and erythrocyte counts

As part of medical treatment, diet should be bland and smooth, without coarse or irritating food substances, and arranged as four or five daily meals The diet may be augmented by mixtures of concentrated protein, minerals, and vitamins such as meretine Good dentures are essential to assure proper mastication Oral sepsis and nasopharyngeal discharges should be eradicated Alcoholic beverages are usually not well tolerated but occasionally wine before meals will arouse the appetite

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SYPHILIS OF THE STOMACH, gummatous or diffusely infiltrative, is seldom symptomatic and, in any case, systemic antiluetic therapy suffices

Gastritis due to leukemia or lymphogranulomatous diseases or associated with uremia, acidosis, portal stasis, or cachexia requires no specific treatment

DIET SCHEDULE FOR CHRONIC GASTRITIS

Breakfast Fresh fruit juice, strained if necessary, or cooked fruit sauce, with no skin or seeds
Eggs, prepared in any manner, fat required should be butter or fresh bacon fat
Bacon crisp parts should be well masticated
Cereal farina, cream of wheat, corn meal, rolled oats cooked all night in double boiler Whole milk or cream, and sugar
White or graham bread plain or toasted, with butter and jelly, or jam or preserves with no rind or seeds, or strained honey
French coffee (*café au lait*), warm milk and coffee, equal parts, weak coffee and cream, cocoa or weak chocolate, hot milk

Lunch and dinner Select foods and apportion quantities to make about two equal meals
Broth or bouillon for atrophic gastritis, perhaps not for hypertrophic gastritis
Cream soup, chowder thick strained pea, corn, bean, or lentil soup
Meat beef, mutton, lamb, chicken, fish, oysters, roasted, baked, or broiled
Potato white or sweet, baked, boiled or mashed
Macaroni, spaghetti, noodles, creamed or simply seasoned with strained tomato juice, boiled rice
Hominy, stewed tomatoes, strained, cauliflower, broccoli, asparagus tips, carrots, baked squash If very young and tender, peas, lima beans, beets, green string beans All vegetables well cooked, to consistency of mashed potato when crushed with fork, or pureed
Greens chopped in food mill or strained through coarse collander, spinach, chard, collards, kale, mustard, beet, and turnip
White or graham bread, plain or toasted, or crusty biscuits, butter, jelly, seedless and skinless jam or preserves
Cottage or cream cheese
Plain gelatin or jello may be used as salad with mayonnaise or French dressing, and tender leaf lettuce
Dessert Gelatin or jello, plain or flavored, soft, partially melted plain icecream, custards, pudding blancmange and similar preparations, plain cake, fruit sauces with no skin or seed
Beverages as for breakfast, weak tea, buttermilk, fruit juice
Seasoning salt, and herbs as basil marjoram, thyme, tarragon, parsley, sage, dill, chives, celery
Dried or powdered preparations are stronger than fresh herbs, but in any form, seasoning of this kind should be added late in the cooking process Several herbs blended are better than a single one used in quantity Strong spices and condiments should not be used

Good appetite is fostered by taste, and attention to what the French call *les fines herbes* will be appreciated and gratifying When appetite is good, the diet is varied, and the quantity of food is adequate, supplementary minerals and vitamins are unnecessary

When gain in weight is desirable, between meal feedings may be planned, consisting of milk or fruit juice with bread and butter or jelly sandwich, plain cake or sugar cookie, or similar articles from the food list Milk may be complemented with one of several powder preparations of protein and carbohydrate, most of which are also fortified with vitamins Meretine is satisfactory. The diet may be modified in fruit and vegetable content according to intestinal function

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PEPTIC ULCER: GASTRIC AND DUODENAL

Therapeutics of simple, benign peptic ulcer comprises symptomatic, restorative, and, preeminently, preventive integrants Complete and continuous abolition of pain is assurance that aggravating disturbance of secretory and motor functions of stomach and duodenum have been altered or controlled and conditions favorable for healing of an ulcer have been established Peptic ulcers originate when the normal secretory, circulatory, and muscular activities of the stomach or duodenum are frequently and persistently deranged Congestion, hyperemia, and engorgement from vasodilatation, or relative ischemia from vasoconstriction, concomitant with depressed formation of protective mucus, and accelerated production of juice with high acid and pepsin content, are conducive to ulceration of stomach

or duodenal mucosa Hypertonicity and hypermotility contribute to the genesis of ulcer

The first stage of an ulcer is circumscribed submucosal or mucosal hemorrhage Many of these absorb, but others are eroded and digested by gastric juice, perhaps become infected, and a chronic ulcer is the consequence The continuous corrosion and digestion by gastric juice promotes chronicity The differences between gastric and duodenal ulcers are due to location and not to inherent peculiarities As cause or effect, the volume of gastric secretion with duodenal ulcer is larger than normal, and the acid and pepsin content is greater With gastric ulcer the stomach secretion may not be unusual in quantity or quality, but is none the less destructive to a vulnerable mucosa The size of the duodenal ulcers is smaller than that of stomach ulcers These circumstances are conditional on the incapacity of the diseased duodenal mucosa to produce the factors required properly to regulate gastric secretion and motility With an ulcer in the stomach, the duodenum is presumptively normal and humoral reflexes are not interrupted or suppressed The regularly alkaline duodenal content is also partially protective Cancer does not occur in the first part of the duodenum frequently, and the rare instances noted in the duodenal loop have not been primarily ulcerous

About 10 per cent of all individuals have, at some time, peptic ulcers The first occurrence is likely to be during the course of, or following, an acute infectious disease, usually of the upper respiratory tract, or after sudden or continuous physical or mental strain Recurrences exacerbations, or complications are also initiated by any of these factors, or by gross indiscretions of diet Original ulcers or early recurrences are prone to heal spontaneously or with simple measures such as rest, vacation, or regulation of diet

Peptic Ulcers in Locations Other Than Stomach and Duodenum Peptic ulcer may form in the lower esophagus, just above the opening into the stomach, presumably in gastric mucosa grown from the cardia An ulcer rarely develops in the second part of the duodenum, with symptoms similar to those of the usual duodenal ulcer, except that nausea is common Stenosis and perforation are infrequent, but hemorrhage may occur Treatment is the same as for duodenal ulcer Peptic ulcer may occur in aberrant gastric mucosa of a Meckel's diverticulum Symptoms may be similar to those of appendicitis, or pain may occur regularly in the periumbilical area late after eating Diarrhea, melena, or abrupt perforation may be the only manifestation The condition is seldom recognized before operation is considered necessary for relief of acute abdominal emergency

Medical Management The rationale of the medical management of peptic ulcer is based on two adequately proved assumptions (1) that gastric juice exerts a deleterious influence upon a defect of the mucosa of the stomach or duodenum, and (2) that the unusually powerful contractions, increased tone and spasm, which occur in the stomach or duodenum when empty, tend to inhibit healing Since these phenomena produce notable discomforts, symptomatic relief and conditions favorable for healing of the lesion may be accomplished by a regimen which counteracts the erosive effect of the gastric secretions and at the same time quiets muscular activity

The basic requirements of such a regimen are met by proper sedation and relaxation together with frequent administration of food and antacid substances By keeping something in the stomach all the time, muscular activity is subdued and secretions are diluted, neutralized, or absorbed

The aliment should be liquid, semisolid, or reduced to a pasty state, without coarse, rough elements Hence, foods which may be finely divided, strained, puréed, or cooked to a soft consistency are chosen Depending on the ingenuity of the physician and the cook and the financial status of the patient, a wide variety is possible The basic foods of most ulcer diets are milk, butter, eggs, gelatin, custard, softened bread or toast, strained fruit juices, and sauces To these are added cream soup, puréed vegetables, chopped or scraped meat or fish, mashed or baked potato, jelly, and similar substances (Table II)

The medicinal agents used in treating peptic ulcer are substances which neutralize the acidity of the gastric juice or by absorption inactivate the acid reaction Most frequently

used have been sodium bicarbonate sodium citrate calcium carbonate calcium or magnesium phosphate bismuth subnitrate or subcarbonate and magnesium oxide Each has advantages and disadvantages

Sodium bicarbonate is soluble and likely to irritate the gastric mucosa and increase acid secretion although initially effective as a neutralizing agent Large amounts of sodium bicarbonate may disturb the acid base balance of the body especially in patients with pyloric obstruction or impaired renal or hepatic function If used continuously the total daily amount should be less than 4 gm *Magnesium oxide* has three times the neutralizing power of sodium bicarbonate and does not form gas but it is laxative and may cause a secondary rise of acid or acidosis *Calcium carbonate* has a low neutralizing value one-fifth that of sodium bicarbonate is insoluble not likely to disturb the acid base equilibrium and is not irritating but may induce constipation or flatulence The phosphate of calcium has similar properties and higher neutralizing capacity but may be irritating *Magnesium trisilicate* has been recommended as an effective antacid neutralization is apparently more prolonged than with other alkaline compounds and adsorbent and antiseptic activities are evident For these reasons magnesium trisilicate may be used as the last medication before sleep

Because of objections to the chemical substances mentioned other materials have been used Colloidal suspension of *aluminum hydroxide* is an effective antacid by absorption and adsorption and is apparently nontoxic and does not disturb the acid base balance of the body When aluminum hydroxide is used with the usual ulcer diet magnesia in some form is required as a laxative Milk of magnesia may be combined with aluminum hydroxide gel Aluminum phosphate in suspension has been recommended instead of aluminum hydroxide particularly for the treatment of postoperative jejunal or stomal ulcers (Table II)

Suspensions of aluminum hydroxide have [illegible] cont n o is drip [illegible] bined with gastric mucin in a recently advocated preparation

A resin *amberlite IR IV* has been tried with results as effective but no better than conventional substances

Protein hydrolysates have been recommended as aids to rapid healing of peptic ulcers The preparations available taste badly and are inconvenient to administer Reported results do not show advantages over other forms of protein customarily used when malnutrition requires attention in the management of a particular patient Concentrated protein resident in the duodenum overstimulates gastric secretion

Enterogastrone extract of mucosa of hogs upper intestinal tract as now used is of no more value than conventional preparations for symptomatic relief and cure of peptic ulcer Enterogastrone administration is directed to prevention of recurrences but sufficient data have not been collected for definitive opinion of the efficacy of the product

An *antispasmodic* or a general sedative or both may be desirable Belladonna or atropine although of rather uncertain pharmacologic effect on gastric activity either motor or secretory is empirically satisfactory Belladonna may be combined with any of the powder preparations as the extract or given separately as atropine tablets or as tincture of belladonna by drops Synthetic antispasmodics are available As a general sedative small amounts of phenobarbital 15 or 30 [illegible] ther [illegible] nes [illegible] ote

p 332)

Acute Ulcer A patient with an acute ulcer should be in bed and the food intake restricted to fluids and semisolids frequently ingested in small amounts A modified Sippy regimen is simple practical and cheap (Table I) The hourly consumption of milk and cream is satisfactory and may be enriched if necessary by one of several protein carbohydrate concentrates reinforced with minerals and vitamins If the patient is obese or cream is not well tolerated skim milk may be used

If the onset of an ulcer or an exacerbation is fulminant with severe pain and vomiting sedatives or opiates may be required before oral feeding is tolerated Effervescent bromide mixtures may suffice but if not retained hypodermic or intravenous barbitu

rates may be necessary Opium derivatives should be withheld until other resources fail, and when mandatory, administered hypodermically in adequate amounts Demerol, 100 mg with codeine sulfate 0 06 gm, should be tried, morphine sulfate in 15, 20, and 30 mg doses, with or without atropine as indicated, is often the eventual recourse Rarely [illegible]

fusion

Perforation Perforation of acute or chronic ulcer demands surgical treatment as soon as recognized For a few cases, if rupture occurred when the stomach was empty, if air is not demonstrable under the dia phragms, and if peritonitis is not evident, conservative management by intragastric suction and supportive measures may be per missible

Hemorrhage After massive hematemesis or melena, and until the status of the patient is determined, absolute physical immobility and mental calm should be assured by 15 mg of morphine sulfate, parenterally administered Grouping and typing of blood should be done immediately, and suitable donors chosen Bleeding into the upper in testinal tract of 90 cc for a relatively short period will produce a recognizably black stool Rapid loss of 1000 cc or more of blood may cause diarrhea with notably red feces Prompt transfusion of whole blood will prevent dilution of circulating blood and dehydration, provide elements essential for clotting, and partially supply nutriment If blood is not available plasma, protein mixtures [illegible]

hours, surgical intervention should be seri ously considered, and if operation is done, a competent surgeon and all equipment, personnel, and adjuvants should be available for gastric resection Unless the exact site of the hemorrhage is known from previous examination, time lost in searching for the bleeding source may be fatal A fibrotic or sclerotic vessel in an old callous scar does not readily retract or close, and is not easily securely tied

Gastroscopic examination may be done safely by a skillful and experienced endoscopist to find a bleeding point in the stomach, or to note reflux of blood from the duodenum through the pylorus

Estimates of hemoglobin and counts of red blood cells are not dependable indices of the extent or duration of hemorrhage Dilution by accessions of tissue fluid or from solutions introduced parenterally, or effects of transfusions of blood, will alter the abso lute and relative amounts of the several constituents of the circulating blood Chemical analysis of the stool for blood yields no enlightening information of the amount of blood lost or termination of the hemorrhage, occult blood may be detected in the feces for days after bleeding has stopped

Blood pressure registers more accurately than hemoglobin estimation the amount and progress of bleeding, circulatory tension should be determined every hour until a stable level is maintained Supportive transfusions of whole blood or other material should be started promptly when systolic pressure is 90 or below All intravenous infusions should be given slowly, as continuous drip, at the rate at which the number of drops per minute sustains peripheral vascular pressure and does not rapidly increase the volume of circulating blood

Oral feeding is begun as soon as the pa tient is quiet and shock condition has been corrected, according to the schedule outlined for acute ulcer (Table I) Gelatin or glucose or both may be added to the milk and cream with advantage, the gelatin may contribute to coagulation The formulas used by Andresen are

Glucose	60 gm
Cream, 20 per cent	120 cc
Milk	880 cc

or.

Gelatin	30 gm
Glucose	60 gm
Cream, 20 per cent	100 cc
Milk	900 cc

These mixtures are kept cool, the one with gelatin not refrigerated, and fed cool or warm in quantities prescribed

Continuous instillation of either of these mixtures, or of milk with aluminum hydroxide, citrated milk, or protein solutions, through indwelling gastric or duodenal tubes, has been advocated for immediate

alimentation after hemorrhage from the stomach or duodenum, but such performance is no more efficacious than frequent oral feeding, and is uncomfortable for the patient and consequently prevents the requisite repose and relaxation

Stools should be kept soft and defecation made easy by mild laxatives, oil, or low rectal enemas Straining to evacuate a hard fecal mass may incite bleeding from a partially or completely clotted source

Meulengracht has since 1931 recommended free feeding for a bleeding peptic ulcer From the first day patients are fed a full pureed diet, including tea, white bread and butter as breakfast, oatmeal porridge with milk, white bread and butter at 9 A M, dinner at 1 P M, milk or cocoa at 3 P M, and *egg, sandwiches of sliced meat or cheese,* and tea at 6 P M The dinner comprises different kinds of gruel, porridge, vegetable soups, meat balls, timbales, chops, omelet, fish balls, vegetables au gratin, meat au gratin, fish au gratin mashed potato, vegetable purées, creamed vegetables, stewed apricots, apple sauce, rice and tapioca puddings Water and milk are served according to the patients' desires

The objective of any method is to replace blood loss, quantitatively and qualitatively, as effectively as possible And to this end, periods of enforced starvation while waiting cessation of hemorrhage, and in fear of aggravation of bleeding, have been abrogated in favor of activities directed to rapid and complete restoration of blood constituents and volume *When ambulant feeding is begun*, ferrous sulfate, 1 0 to 1 5 gm daily, may be given

Roentgen examination to locate the source of bleeding should be deferred until after the hemorrhage has ceased so that dislodging a clot by the heavy barium suspension and *manipulation* is improbable When painless [illegible]

rim of inflammatory *edema When the* existence and site of an ulcer are known investigation may be delayed *When reasons* prevail to bring into consideration cancer of the stomach as the origin of hematemesis or melena prompt roentgen or gastroscopic examination may be advisable.

Obstruction and Retention *The stomach* may not empty properly because of cicatricial stenosis of the duodenum, obstruction by inflammatory edema often with coincident spasm, or from interference with gastric motor function by a saddle ulcer on the lesser curvature In any cases of obstruction or retention the management is basically that of an acute ulcer That is, the patient should be in a hospital, in bed, and the stomach should be completely emptied by tubal aspiration and lavage The large Ewald tube with suction bulb is probably the simplest apparatus for initial evacuation of the stomach Thereafter feedings as prescribed for acute ulcer are instituted (Table I)

Stomach contents are thoroughly removed 3 hours after the last feeding each day and *the amount recovered is measured and recorded* If the quantity of gastric residue progressively diminishes, and the patient is quiet and comfortable, the program may be continued as designed for acute ulcer, under the assumption that the inflammation and spasm are subsiding If, after 5 to 7 days, the stomach retains as much or more than before treatment began, organic, mechanical, permanent obstruction may be presumed and *operative intervention considered* necessary Adjunctive measures may be required for sedation and local relaxation Combinations of phenobarbital and belladonna or atropine are as satisfactory as any of the synthetic preparations

An indwelling intranasal tube may be introduced into the stomach or duodenum *through which feeding mixtures* and antacids are instilled The flow of nutrient or solution is stopped periodically and, after a suitable interval, suction applied The quantity of stomach residue aspirated determines the amount of subsequent feedings, and the permanence or recession of the obstruction However, the objections made to intubation for treatment of hemorrhage or acute ulcer apply to instances of obstruction The intranasal tube is an annoyance and the discomfort annuls the theoretical benefits

When the course of events with uncomplicated acute ulcer, with bleeding ulcer, or with obstruction or retention is favorable, medical management may proceed through 3 weeks, and an ambulant program begun the 22nd day (Table II)

Ambulant Management. An ambulatory regimen is applicable for most of the patients with simple, uncomplicated, benign peptic ulcer Instructions should be specific and preferably printed in some form that may be given to patients The purposes and objectives of the diet and medication should be explained in plain terms After trial of the standard program for 10 to 14 days, the patient should report results, residual symptoms, and discuss articles of food habitually eaten but not mentioned in the list issued Adjustments for the individual are made at this time and the modified schedule is continued for 6 weeks

After approximately 8 weeks from start of treatment, radiologic observation of results is made At this time a simple ulcer has healed and medication is gradually stopped, No 1 first, then No 3, and finally No 2 If discomfort is felt when No 3 is eliminated the accustomed dose should be resumed Sufficient amounts of No 2 should be taken as necessary for regulation of bowel function Usually the antacids and correctives are readily suspended and a protective diet of three equal meals with glasses of milk between suffices for several months If a sedative antispasmodic prescription has been necessary, this should be continued Vegetables need not be puréed if amenable to softening by cooking, but should not be served raw Fruits with skins and seeds should be cooked and strained Meat should be grilled, broiled, or roasted, not fried, stewed, or boiled

The patient is advised to revert to a strict ulcer regimen during colds, any acute febrile disease, or when unavoidably subjected to continuous fatigue, mental strain, or emotional disturbance At this point the physician should be well acquainted with the patient's personality, environment, and reactions to problems and conflicts, and be prepared to plan and advise conduct that may prevent exacerbation of the ulcer or recurrent consequences

Treatment of peptic ulcer must be treatment of the individual Many factors influence unfavorably the fate of a particular patient Fatigue and exposure, infections, anxiety, grief, emotional shock, and inability to eat proper food at regular intervals may

toration of domestic tranquility, solution of an emotional or financial problem, elimination of sources of repeated infectious insults, protection against excessive fatigue may be more important than details of medical management or technic of surgical treatment An environmental conflict may compel an individual to behave against his natural inclinations with consequent resentment, psychic turmoil deranges secretory, circulatory, and motor controls in general and, in some, of the gastro intestinal tract in particular This consideration is the basis for explaining peptic ulcer in terms of somatic manifestations of psychoneurosis Peptic ulcer is not fundamentally a psychosomatic disease, but

complete, successful treatment of a particular patient

Medical treatment often fails because the patient cannot or will not co operate Medical programs carelessly planned and indifferently supervised are doomed to failure An ulcer may be apparently refractive because the host is recalcitrant or because the directing physician is ignorant or incompetent Under these circumstances the assumption of intractability of the ulcer is not valid and resorting to surgery will not be justified

Surgical Treatment. Surgery demands consideration in medical therapy of peptic ulcer, not in respect of technic, but of policy That is, sound medical judgment should determine when and under what circumstances surgical intervention should be made in a particular instance The decision concerns the summary of the course and the momentary status of the individual ulcer

Perforation as the first event, or consequent to penetration of a chronic gastric or duodenal ulcer, requires surgical treatment, methodically qualified as discussed After perforation of a duodenal ulcer, symptoms recur in 60 to 65 per cent of cases, with gastric ulcer, sequelae appear after seven or eight perforations A penetrating ulcer with the base of a crater adherent to, or actually

formed by tissue of an adjacent organ usually the pancreas or liver will not heal and requires surgery Proved mechanical duodenal obstruction by a stenotic cicatrice obviously must be surgically relieved For old people simple gastro enterostomy is satisfactory Hourglass contracture of the stomach caused by the chronic fibrotic ulcer can be corrected only by surgical means

For continuous bleeding after 48 hours in patients over 45 years of age surgical exploration is probably advisable But in this event facilities and preparations for gastroduodenal resection must be assured Search for source of bleeding contemplating ligation of a vessel is futile

The value of a surgical procedure for non obstructive benign recurrent duodenal ulcer which has not bled is debatable Simple gastrojejunostomy has been abandoned except for special cases A satisfactory operation for peptic ulcer is resection of 75 per cent of the distal part of the stomach and the first part of the duodenum according to the Hofmeister or Billroth II technic with a short loop reverse jejunostomy When a duodenal ulcer is irremovably fixed to adjacent organs the pyloric antrum in such case should be excised with three fourths of the body of the stomach

Vagotomy or section of all branches of the vagus nerve accessible below the diaphragm with or without gastro enterostomy is currently advocated for chronic duodenal ulcer of young or middle aged adults Eventual result [illegible]
or below [illegible]
from dat [illegible]
motility has been an unfortunate consequence of many vagotomies Addition of vagotomy to the operation of subtotal gastrectomy is of slight value and that only to prevent possible recurrences Most of the [illegible]

bined with gastrojejunostomy is not advisable for ulcer of the stomach in any event *A gastric ulcer which does not heal with competent medical treatment is probably malignant and requires extirpation by partial gastro duodenal resection*

Subdiaphragmatic section of the vagus nerve is applicable in instances of recurrent ulceration or hemorrhage after gastro enterostomy or partial gastric resection

Gastrocolic fistula as a consequence of penetrating postoperative jejunal ulcer is a surgical problem

Gastritis — superficial catarrhal hypertrophic and atrophic—is seen through the gastroscope in stomachs after gastrojejunostomies or in gastric pouches after partial or subtotal resections When the diet is properly regulated this form of mixed gastritis is seldom conducive of symptoms

Other unfortunate sequelae of gastric resection are due to rapid emptying through the artificial stoma Caused either by direct stimulation of excessive insulin secretion from the presence of abundant food substance in the jejunum or by more complex mechanisms initiated by intestinal distention physical sensations attributable to hyperglycemia and splanchnic vascular disturbance frequently occur soon after meals Also [illegible]
glyc [illegible]
the [illegible]
after eating Either of these syndromes or both may occur in one patient and may be corrected by frequent feedings of small quantities of food preferably protein in composition

Ulcer is such a common ailment afflicting so many people and causing so much disability that any physician attempting to treat it should carefully study the whole ulcer problem and the individual concerned in order to apply the best judgment in management No other disease demands such close doctor patient relationship

An editorial in the *British Medical Journal* states that the medical profession has learned too slowly that neither the dramatic intervention of surgery nor the elaborate ritual of the alkaline diet can banish the constitutional tendency to peptic ulceration To separate the ulcer patient from his diathesis is like severing the fisherman from his soul and until some new secret of nature is revealed the patient must be taught how best to live at peace with his ulcer And to do this he must learn how to live at peace with him self

TABLE I

Basic Management for Acute Peptic Ulcer

(This Program May Be Administered at Home with Competent Attendants)

First week Three ounces of ½ milk and ½ cream every hour 7 A M to 9 P M If cream is not well tolerated whole milk 3 oz (90 cc) each feeding or skimmed milk with a powdered compound of protein and carbohydrate added 1 part of powder to 6 or 8 parts of milk by volume may be used Most of these preparations contain minerals and vitamins Dietene or Meritine are examples

Second week Eighth day add one egg poached or soft boiled to 12 o clock feeding and a small saucer of cooked cereal (cream of wheat farina) at 8 A M and 6 P M

10th day add one piece buttered toast to 10 A M and 4 P M feedings and a soft boiled or poached egg at 2 P M

12th day add one soft boiled or poached egg to 8 P M feeding and gelatin (jello) at 9 A M and 1 P M

Tl

P M and plain icecream at 7 P M

11 30 A M 1 P M 2 30 P M 4 P M 7 P M 9 P M and add at 7 A M egg and toast at 8 30 A M cereal at 10 A M milk jello with cream and plain sugar cookie at 11 30 A M cream soup and soda crackers at 1 P M egg and toast at 2 30 P M rice or tapioca custard and plain cookie at 4 P M icecream and plain cookie at 5 30 P M puréed vegetable † egg and toast at 7 P M potato with butter at 9 P M cooked strained fruit sauce and plain cookie

If pain occurs between feedings 1 or 2 teaspoonfuls of suspension of aluminum hy

stipation magnesium oxide or milk of magnesia may be prescribed in appropriate amounts

TABLE II

Ambulatory Schedule

7 A M I tablespoonful No 1 * in half a glass of water

7 30 A M Strained fruit juice or fruit sauce baked apple without skin seeds or core
Soft boiled egg with one slice buttered toast or poached egg on toast
Cooked cereal (cream of wheat or farina) with cream and sugar
Glass whole milk heated or cool

8 30 A M Half a teaspoonful No 2 ** with ½ glass of water

10 A M Glass whole milk or milk with protein carbohydrate powder added

11 A M Two teaspoonfuls No 3 *** in a glass of water

12 30 P M Cream soup
White bread or rolls buttered
Vegetable pureed strained or mashed †
Baked or mashed potato boiled rice

* No 1 is kaolin and aluminum hydroxide (Kaomagma)

** No 2 is a powder composed of calcium carbonate calcium phosphate and heavy calcined magnesia (magnesium oxide) in proportions adjusted to indi idual requirements of bowel funct on

*** No 3 is alum num hydrox de (amphojel) or alum num phosphate (pl osphajel) or mixture of aluminum hydroxide and magnes um tris l cate preparations may be taken in tablet form if l quids

radical change n usual diet If the laxative is not

† Vegetables with shells (beans corn) or seeds (tomato) should be well cooked and stra ned those with husk (peas) may be puréed others with skin or stalks that may be remo ed (carrots cauliflower asparagus) may be well boiled and mashed

For package lunches sandwiches may be made of bread and butter with cream cl eese jelly

few pinches of cocoa powder

macaroni, spaghetti, or noodles, with butter or vegetable juice
Custard pudding, with rice, tapioca or bread, jello with cream and sugar
Cooked, strained fruit sauce or plain ice-cream
White cake, angel food, sponge cake, or sugar cookies
Glass whole milk
1 30 P M Half a teaspoonful No 2 ** with ½ glass of water
3 P M Same as at 10 A M
4 30 P M Two teaspoonfuls No 3 *** in ½ glass of water
6 P M Same as 12 30 P M with addition of broiled or roasted beef, mutton, lamb, fish, chicken, turkey, squab, guinea hen, calf liver, sweetbread, or oyster
7 30 P M Half a teaspoonful No 2 ** with ½ glass of water
9 P M Two teaspoonfuls No 3 *** in ½ glass of water
At bedtime glass of milk with bread and butter, and jelly or cream cheese sandwich, cottage cheese, plain sugar cookie or graham cracker, or fortified milk, or half a glass of water with 2 teaspoonfuls of No 3

necessary, No 1 or No 3 should be substituted at hours designated for No 2, that is, something must be taken as scheduled

These diets may require modification for patients with heart or kidney disease, diabetes mellitus or obesity Actually, association of peptic ulcer with other systemic disease, particularly diabetes is rare.

JAMES B CAREY

During the past few months, following completion of the preceding discussion of peptic ulcer, there has been renewed interest in the use of autonomic blocking agents in the treatment of ulcer In an effort to diminish gastric secretion and to decrease motility of the gastro intestinal tract several cholinergic blocking agents have been tried with little success However the development of methantheline bromide (B diethylaminoethylxanthene 9-carboxylate methobromide), marketed under the trade name of Banthine may prove to be the type of drug long sought in ulcer management It is too early for accurate evaluation but several observers * have indicated that this preparation is a valuable addition to drug therapy of peptic ulcer

The drug is usually prescribed in 50 to 100 mg doses every 6 hours day and night during the acute stage After healing is well in progress the dosage may be lowered, but administration of the drug every 6 hours must continue indefinitely

It must be emphasized that this drug is only an adjunct to the usual measures of diet rest and relaxation and its true usefulness will need more time for accurate evaluation —*Editor*

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DISEASES OF THE SMALL BOWEL AND COLON

REGIONAL ENTERITIS

A subacute or chronic destructive, exudative, and proliferative regional inflammatory process has been observed in the small intestine from time to time by clinicians, roentgenologists, and surgeons This condition was well described by the late Dr William J Mayo as long ago as 1893 For many years it was thought that the lesion was limited to the distal part of the ileum and even in the rather accurate description of the condition by Crohn, Ginzburg, and Oppenheimer in 1932, the impression is given that the lesion is limited to the distal part of the ileum or to the bowel contingent to the distal part of the ileum, or to both However, a similar pathologic process has been found to involve, although somewhat less frequently, all segments of the small intestine, and to be localized high in the jejunum as well as in the distal part of the ileum

Treatment. For the present, treatment varies for the localized granulomatous form of regional enteritis, the extensive ulcerative form, and the recurrent lesions.

The treatment of the granulomatous enteritis in its localized form is largely surgical Ileocolostomy and subsequent resection of the diseased segment of the bowel are the treatment of choice However, when to operate and how extensively to resect are questions that only experience and long follow up can answer It is definitely not wise to operate during the acute or subacute phase of the disease It is here that the medical treatment becomes particularly important. Adequate rest, a low residue diet, and the administra-

tion of one of the sulfonamides should be continued until the patient is free of fever, the tenderness in the abdomen has largely subsided, and the acute infectious phase has been overcome

So far the sulfonamide drugs of choice for use in these cases have been succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathaladine) Administration of 12 gm of sulfasuxidine, in divided doses of 30 grains (2 gm) every 4 hours or of 120 grains (8 gm) of sulfathaladine in a similar manner has often been followed by a prompt subsidence of the acute and active symptoms If the condition is of the localized granulomatous process, then surgical intervention should be carried out as soon as the acute symptoms subside and the patient's condition warrants

What has been said about the medical treatment for the localized disease should be adhered to more generally and for longer periods in cases in which the disease is of the ulcerative type For such cases it may be wise to continue the medical management for weeks or months as follows the sulfonamide drugs should be taken for a period of 2 weeks, then the patient should have a week of rest, and then treatment with the drugs should begin again Streptomycin has been helpful in some of these cases It can be given in divided doses averaging a total of 2 gm a day There is some evidence that the combination of streptomycin and sulfathaladine each in smaller amounts than those mentioned has greater value than either one alone When the condition has become quiescent and there is no evidence of spreading, surgical intervention may be advisable in a fair number of these cases

Recurrence of the localized granulomatous type of the disease after resection is rare, but recurrence of the extensive ulcerative type is common This fact makes it necessary to consider the third part of the program of therapy Roentgen therapy has been used for recurrent regional ileitis for a number of years Early impressions indicate that it is a reasonable and satisfactory palliative procedure Although the technical procedure of treatment is not too well established, it seems advisable to expose the entire abdomen to roentgen rays at a moderate voltage The dosage is the same as that commonly used in treatment of chronic inflammatory conditions.

Treatment with roentgen rays has produced striking results in selected cases It was first applied in treatment of recurrent lesions when resection did not seem advisable As experience grew it was used in earlier cases and particularly in cases of the ulcerative form

If the disease recurs even though the recurrent involvement may not be especially extensive, there seems to be some secondary effect on intestinal absorption so that eventually [illegible]
mark [illegible]
in p [illegible]
least 140 gm or more of protein a day It should be low in residue In addition, in cases of recurrence in which steatorrhea is present, the diet should be low in fat, similar to the diet for sprue Striking changes for the better have frequently been noted when fat is eliminated from the diet and the patient is given a diet high in protein Excessive amounts of vitamin B complex as well as generous amounts of other vitamins, particularly vitamins A, C, and K, have been helpful in keeping these patients in good condition Doses of 100,000 international units of vitamin A, 200 mg of vitamin C, and 4 to 6 mg of vitamin K should be given daily Various preparations of amino acids given by mouth in large amounts have been particularly helpful in giving these patients adequate amounts of protein It is essential that a preparation be chosen which contains all the essential amino acids Unless this is done their administration will be useless

Prognosis The prognosis for patients who have granulomatous ileitis is good after resection for, in general, less than 5 per cent have recurrences However, among patients who have the ulcerative form of the disease the rate of recurrence is high and is probably nearly 20 per cent, or even more For patients who have ulcerative lesions then, all reasonable measures of treatment must be invoked It is of particular interest to note that such patients may have had a resection and may have remained well for 10 to 12 [illegible]

as during the recent war, recurrence may

take place It is obvious that these recurrences are not due to the fact that enough tissue is not resected There must be some smoldering infection in the lymph nodes of these individuals or a latent infection some where in the abdomen which remains under control for some time and then when resistance is lowered, it flares up again This all points to the fact that perhaps if the cause of the disease were known its final treatment would be better understood

J Arnold Bargen

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ALIMENTARY TUBERCULOSIS

Tuberculosis is probably the oldest known cause of dysentery Tuberculous colitis is part of the intestinal involvement that occurs secondary to tuberculous disease of the lungs or other bodily structures It is a serious complication *In most cases the primary tuberculous* lesion is situated in the lungs

The disease can be divided into two clinical types (1) the ulcerative type and (2) the hyperplastic type The former usually occurs in the course of active pulmonary disease The latter may occur as a late sequel of an otherwise quiescent pulmonary lesion and may even occur without the presence of the pulmonary tuberculosis being proved

Management Since the two forms of this disease as they affect the intestine are different pathologically, the program of management also will be different By and large, it can be said that tuberculosis is essentially a medical disease regardless of the site of the lesion, however surgical measures are used as an adjunct to careful medical supervision There is no specific treatment for ulcerative intestinal tuberculosis

Since the success of treatment is largely dependent on the stage of the disease at which the diagnosis is made, the importance of early diagnosis cannot be stressed too *strongly As soon as the* presence of an intestinal lesion is suspected, the chief objective of treatment should be to take as much of the burden as possible off the inflamed and handicapped bowel

A smooth diet of rather low residue is indicated It may be wise to suspend the forcing of food It is probably a good plan to use this type of treatment in any case in which the presence of an intestinal lesion is suspected Roughage should be eliminated from the diet as far as possible Fresh fruit juices and purées should replace the more fibrous raw fruits, vegetables, and salads Raw milk

The diet outlined for patients who have chronic ulcerative colitis *will be applicable* in most cases of intestinal tuberculosis

Phthisiologists frequently have mentioned the importance of adequate vitamins in the diet as well as the value of increased amounts of protein foods Extra amounts of cod liver *oil citrus fruits, and, particularly, tomato* juice have been advocated and their use has resulted in a marked reduction of intestinal symptoms and a great gain of weight When constipation is disturbing some soft bulk *may be added*

Colonic irrigations with physiologic solution of sodium chloride and so called intestinal antiseptics have been used and seem to be worth while for their cleansing qualities when diarrhea is *severe If given as* warm enemas, at bedtime, they may afford the patient more rest and sleep

Rest, as in all forms of tuberculosis is the keystone of treatment The patient should be in bed *until he is afebrile and until symptoms* of dyspepsia have disappeared, then carefully graded activity is in order

Injection of oxygen into the peritoneal cavity has been advised and in selected cases has produced good results *Roentgen therapy* also has proved beneficial in some cases

Heliotherapy, cautiously applied over parts of the body and finally over the whole body, is useful This type of therapy is generally accepted by all *who have had* extensive experience in treating this condition Ultraviolet light seems to have value and in the hands of some workers the effects of this

type of therapy have been found superior to those of sunlight

Many drugs such as compounds of arsenic calcium and mercury have been used Thus acetarsone (acetylamino hydroxyphenyl ar sonic acid) and treparsol (formyl amide of meta aminopara oxyphenylarsonic acid) have their advocates Calcium gluconate and a solution of parathyroid and calcium chloride have been injected intravenously over long periods For the active diarrhea the ordinary drugs recommended in the chapter on thrombo ulcerative colitis are indicated

As with other forms of ulcerative colitis some of the drugs of the sulfonamide series have received experimental and clinical trial Of the drugs that have been administered to modify inhibit or prevent tuberculosis in guinea pigs sulfanilamide sulfapyridine azosulfamide promin (sodium p p diamino diphenylsulfone N N didextrose sulfonate) and some other drugs which have been in troduced more recently have produced satis factory results The dosage of these drugs must be individualized for each patient

Many drugs have been given in the hope that they might have a specific effect on the tuberculous process Some years ago promin gave hope because of its favorable modifica tion of the course of tuberculosis experi mentally produced in guinea pigs However later studies did not justify the earlier hopes With the advent of the antibiotics these were tried successively It has been shown that streptomycin or dihydrostreptomycin 2

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in pulmonary and renal disease but favorable results also have been obtained in some cases of intestinal tuberculosis Finally as in pulmonary tuberculosis care in a sanatorium is definitely indicated in cases of ulcerative tuberculosis of the intestine There is con

gators have advised operation in the ulcera tive form of tuberculosis if and when the pulmonary condition is satisfactory or qui escent Argentine investigators particularly favor this course and during a recent visit to Buenos Aires the writer saw the results of such treatment and observed an operation in which the ileum was completely transected and then transplanted into the colon below the diseased segment The involved segment is not removed surgically nor is its removal advocated Observation of patients for a number of years after they have been treated in this manner has indicated that this type of treatment may be of value

In the case of the hyperplastic form of tuberculosis when this lesion involves a local segment of bowel as it usually does intesti nal resection or at least diversion of the fecal stream by ileocolostomy or colocolostomy is the treatment of choice This type of tu berculosis often causes obstruction partial or severe and by interfering with digestion impedes healing of a smouldering pulmonary lesion When obstruction is relieved by a short circuiting operation the lung will be given greater opportunity to heal In some cases after this type of surgical treatment the lesion in the segment of the bowel which no longer functions will tend to dry up and heal However secondary resection usually will be indicated

Illustrative Case A married woman aged 48 years came to the Mayo Clinic on Sept 29 1941 because of pain in the right lower abdomi nal quadrant episodes of intestinal obstruction weakness and loss of weight of a year s dura tion Although these symptoms had been pres ent for that length of time they had been much worse in the 6 months before the patient came to the clinic In April 1941 she had suffered from severe pain in the abdomen and nausea and vomiting These symptoms had lasted for 6 days and during that time she had not had any bowel movement and had not passed any gas She had had several similar attacks in the subsequent months with periods of loose stools between the attacks

On admission she weighed 94 lbs (42 6 kg) whereas her normal weight the year before had been 120 lbs (54 4 kg) Her temperature was 98° F Numerous stools were examined No unusual parasites ova bacteria or acid fast or gran m e e fo nd The o l f

normal The sedimentation rate of the erythro cytes was 48 mm in one hour The values for the total acid and the free hydrochloric acid in the gastric contents were 56 and 38 respec tively when determined by the method of Topfer Roentgenologic examination with a bar

ium enema revealed a long tumefactive lesion which involved the cecum ascending colon and the terminal portion of the ileum This did not have the appearance of any specific inflammatory process There was no unusual hyperirritability of this segment of the bowel It was felt that the lesion might be a tuberculoma or amebic granuloma The administration of 4 grains (0 26 gm) of emetine hydrochloride in divided doses and 46 grains (3 gm) of treparsol during a period of 4 days did not have any effect on the symptoms or on the roentgenologic appearance of the lesion The tenderness in the right lower quadrant of the abdomen persisted Ileocolostomy was performed for what was described as a large inflammatory granuloma Two lymph nodes from the adjacent mesentery were

the cecum and ascending colon was performed for ulcerating and hyperplastic tuberculosis of these portions of the intestine The patient made an uneventful recovery

This case illustrates that tuberculosis can *exist in the intestine as a primary process* without evidence of tuberculosis elsewhere in the body

Treatment of Complications For some of the complications surgical intervention occasionally will be indicated When such is the case, treatment will have to be individualized and the complication considered as a disease apart from the basic lesion

J ARNOLD BARGEN

REFERENCE

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CHRONIC THROMBO ULCERATIVE (STREPTOCOCCAL) COLITIS

Since uncertainty regarding the cause of some forms of ulcerative colitis still exists, it seems particularly important to set forth clearly the nature of the ulcerative colitis under consideration when therapy is being considered

In this article we shall consider that form of ulcerative colitis which has its inception in the most distal portion of the wall of the rectum and spreads relentlessly orad from that point This disease involves the wall of the bowel, the mucous membrane is involved only secondarily Involvement is diffuse The disease begins in the submucosal structures as a thrombotic process and produces a granular, easily bleeding edematous mucous membrane, diffuse narrowing of the intes

defined group of symptoms, varying with the progression of the disease and the interjection of various complications and sequelae which may be associated with or follow the progressive, *destructive process* Rectal bleeding is a pathognomonic sign The amount and severity of the bleeding will *vary with the extent of involvement* and with the rapidity of its progression If the involvement is extensive, diarrhea and dysentery will be severe When an attack occurs in a fulminating manner, the patient may be overwhelmed by a combination of these symptoms and signs This condition has been commonly designated as "thrombo ulcerative colitis," or as 'streptococcal ulcerative colitis"

The large majority of patients suffering

tion between internist and surgeon is so valuable as it is among patients afflicted with this malady In the last decade, the attitude of physicians toward the disease has changed from one of hopelessness and despair to one of hopefulness and accomplishment

It is well to think of this disease as the modern practitioner thinks of tuberculosis One should not speak of its cure but of its control

This is a disease in which wise guidance of the patient by the general practitioner for a long period is essential Treatment should be based on the following convictions (1) that the condition is an infectious disease of the large intestine, (2) that uncomplicated thrombo ulcerative colitis is a medical problem, and (3) that certain complications are definite indications for operation

Medical Treatment In cases of thrombo-ulcerative colitis in which such complications as neoplasm, polyposis, stricture, perirectal abscess, perforation, or nephrolithiasis do not exist, the disease is a medical problem

Moreover most of the other complications described fall in the realm of the internist

Rest and Restful Recreation —In acute fulminating thrombo ulcerative colitis rest in bed and absolute quiet should be main tained until the patient is free of fever and then there should be a gradual return to physical activity To rest the intestinal tract it may be necessary to withhold food by mouth and to give fluids parenterally In the more chronic but severe type of the disease without fever restful recreation is important By this is meant that the patient should not be kept in bed but should follow a positive program of mild activity Reading short walks and mental diversion are helpful Pa tients who have the disease become dis couraged easily The slightest change of symptoms which is not for the better may undo days of improvement because of the patient s mental attitude toward such a change Patience and perseverance on the part of the physician and an optimistic viewpoint are essential Occupational ther apy in many forms can be made interesting This type of diversion is invaluable for it tends to distract the attention of the patient from his need of remaining near a toilet room

Diet The feeding of patients who have this disease is one of the most difficult dietary problems in medicine It seems that in the past many physicians have too greatly re stricted the amount of food allowed these patients and as a result the patients have lost strength and their ability to fight the infec tion In the active stage of the disease there is invariably a lagging of appetite or com plete anorexia The problem then is first one of creating an appetite and next one of giving foods which are digested almost en tirely in the stomach and small intestine and which thus leave little residue in the colon The foods prescribed should vary with the stage severity and complications of the dis ease When the symptoms are acute the patient may be able to take only a small amount of highly concentrated food In cases in which the disease is more severe it may be necessary for a time to give nothing but liquids by mouth In the cases in which the disease is particularly severe a solution of 5 or 10 per cent dextrose can be injected intravenously and large amounts of physio logic solution of sodium chloride can be injected under the skin

In the average case however the essential features to be considered in the diet are that it shall not be irritating that it shall be of low residue that it shall have an adequate content of calories proteins vitamins and minerals and that it shall be offered as attractively as possible Some of the foods of low residue are lean meats rice white bread Italian pastes sugar well cooked and strained cereals cooked eggs butter and cream Proteins in most forms are desirable Vitamins can be supplied in concentrated form in fruit juices yeast butter wheat germ cod liver oil or irradiated ergosterol Contrary to the usual assumption milk is not a low residue food and it is not well

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patients in the hospital where their activi ties can be controlled accurately even though they may not be acutely ill On this basis a definite dietary program has been outlined On admission the patient is given strictly bland food to which additions are made at regular intervals One may start at various stages of this program but few patients will tolerate the full diet from the beginning

Additions to the foundation diet will re sult in a full diet containing 140 gm of protein and 3 400 calories Jelly or jams without seeds may be served if desired Beverages should not be iced but rather should be lukewarm Icecream should be eaten slowly Condiments such as mustard horse radish catsup vinegar and highly sea soned sauces or relishes are best avoided

Although the diet is thus based on broad general principles it must still be made in dividual for as with many other conditions few patients react similarly to any given program It must be graded up or down to fit individual needs Occasionally in the late stages of the disease peripheral neuritis has been noted and patients so afflicted will respond dramatically to the administration of large amounts of thiamine chloride In a few cases marked reduction of dark adaptation has been noted This can be relieved by the administration of large amounts of vitamin A At times as much as 100 000 international units has been given daily M

there will be marked reduction of the ascorbic acid content of the blood serum because the patients have been afraid to take adequate quantities of citrus fruits Such patients are aided materially by being given extra amounts (200 to 300 mg daily) of *synthetic vitamin C in tablet form* Finally, there is the rare patient who has one or several massive hemorrhages because of a reduction of the concentration of prothrombin in his blood Such a patient receives dramatic relief by being given vitamin K, either by mouth or by vein Klotogen (vitamin K concentrate in peanut oil) or menadione (2 methyl 1 4 naphthoquinone) may be administered Klotogen may be obtained in capsules, each of which contains 1000 units of vitamin concentrate From 6 to 9 of these capsules may be administered daily Menadione bisulfite may be administered intra*venously in doses of 1 grain (0 065 gm)*

Except in these unusual situations, vitamin concentrates are used only to assure that the diet will not be lacking in any of these

VACCINE When improvement occurs, and in cases in which the disease is mild or is observed early, a bacterin, prepared as an autogenous vaccine from the organisms found in the rectal ulcers in each case, is administered subcutaneously This is given every 3 to 5 days for several months The initial dose is 0 1 cc and each succeeding dose is increased 0 1 cc until the patient is *receiving 1 5 cc After a rest of several* months, the same procedure is repeated Three or four such courses of treatment are administered, or *the vaccine is given until* the patient is free of symptoms After that an occasional course of vaccine is given for several years

NURSING CARE Most of the patients who have this type of colitis are so ill that hospitalization is advisable Rest in bed usually is prescribed for the initial part of the treatment, and often for weeks during an acute exacerbation The systemic execution of the many details necessary for comfort and peace of mind, as well as for actual physical progress, can be accomplished only by careful nursing which may be by the hospital staff or by helpful *persons in the patient*s home Freedom from worry and emotional strain is important Fatigue and *nervous excitability interfere with a patient*s progress It is important to keep the patient warm and to maintain the fluid balance Occasionally, hot abdominal stupes seem to give much comfort The great urgency of movement of the bowels and the straining at the stool must be allayed This can be done by judicious psychotherapy Sufficient sleep is most helpful The many little comforts which are accorded patients who have any serious illness cannot be overemphasized in these cases

DRUGS Tincture of opium may be given in minimal amounts The deodorized tincture can be g*iven in doses of 5 to 10 minims (0 3* to 0 6 cc) three or four times a day It is best given for only 4 or 5 days in succession *After its administration has been discon*tinued for a few days, it may be administered again and then stopped as soon as possible

Tincture of iodine (7 per cent tincture of iodine U S P XII) can be given in doses of 10 to 15 minims (0 6 to 1 cc) in a glass of water after meals It usually should not be administered longer than a week but if it seems to help in reducing the number of rectal discharges and results in general well being its administration may be resumed after a rest period of a week

Among the sulfonamide drugs which have been found useful in the treatment of this disease are azosulfamide (disodium 4 sulfamido-phenyl-2 azo-7-acetylamino 1 hydroxy naphthalene 3, 6 disulfonic acid) and various derivatives of sulfathiazole These drugs preferably should be adminis*tered in courses After the* drug has been administered for 2 weeks, its administration should be discontinued for one week At the *end of this period, the administration* of the drug should be started again and continued for another 2 weeks When azosulfamide is administered in *this manner to an average* adult, 60 to 90 grains (4 to 6 gm) of the drug can be administered in divided doses in 24 hours *For children the dose* will be correspondingly smaller Phthalylsulfathiazole (2 N[4] phthalyl sulfanilamido-thiazole) may be given in *doses of from 120 to 240* grains (8 to 16 gm) in 24 hours

Although the toxicity of both of these drugs is low toxic reactions have been known to occur even with these sulfonamides When either of these drugs but particularly the former is being administered it is important to have the concentration of hemoglobin the erythrocyte count and the leukocyte count checked frequently since anemia is likely to occur without other symptoms of toxicity

Although sulfathiazole usually is well tolerated when a total dose of 45 to 75 grains (3 to 5 gm) is administered daily it is more likely to produce toxic effects than is azosulfamide or phthalylsulfathiazole

Since it has been observed that rheumatic fever and severe ulcerative colitis are similar in some respects various preparations of salicylic acid have been administered in the *treatment of ulcerative colitis* Investigators have tried to prepare combinations of the sulfonamide drugs and preparations of salicylic acid Salazopyrin (salicyl azo sulfapyridine) is an example of such a combination *
[illegible]
divided doses in the same way as the other sulfonamide drugs are administered

In cases of acute fulminating ulcerative colitis some of the other sulfonamide drugs such as sulfadiazine are indicated They should be administered in suitable concentrates so that a concentration of at least 12 to 15 mg of the drug per 100 cc of blood will be maintained A striking effect has followed the administration of all of these drugs in selected cases The best results will be obtained when the administration of the drug is started early in the course of the disease

Several antibiotics have received a clinical trial in cases of active ulcerative colitis The only one that has proved useful in the treatment of this disease is penicillin It is chiefly of value in cases in which the patients are very ill In many cases in which the disease has been acute and has caused a high fever the passage of many bloody purulent stools rapid wasting and all the concomitants of a severe debilitating illness the intramuscular administration of 50 000 to 60 000 units of penicillin every 3 hours has resulted in dramatic control of the symptoms The administration of penicillin should be continued for at least 10 days to 2 weeks As much as 100 000 units of penicillin has been administered every 3 hours by the intramuscular route in the treatment of some patients Recently a few patients have received the calcium salt of penicillin by the oral route Likewise on occasion penicillin in the form of rectal suppositories has been used To date the latter two methods of administration have proved of little or no value in the treatment of the seriously ill patients

Up to the present streptomycin has not proved of value in the treatment of this infection *

Oxygen With the advent of the BLB mask which made it possible to administer oxygen in concentrations up to 100 per cent in an easy manner efforts were made to control the critical stage of this disease with oxygen In a few cases the administration has produced immediate relief which has been striking From a severe toxemic state with high fever rapid thready pulse and cyanosis the patient s condition has been changed to one of comfort with temperature receding and fingers returning to normal color All in all results parallel to those obtained in pneumonia have been achieved now and then

Transfusion of Blood In some cases the value of blood transfusions is inestimable Blood may be given for several reasons (1) in cases of severe sepsis and depletion to fight the toxemia (2) for anemia and the weakness following loss of blood (3) for hypoproteinemia and (4) for general debility from longstanding disease Two to five transfusions of 150 to 250 cc each, have [illegible]

Irrigations and Instillations Our experience as well as that of many other clinicians

* This drug is manufactured by A B Pharmacia Stockholm Sweden

* Since this article was written the use of the adrenocorticotropic hormone ACTH has been found to be of definite value in this type of ulcerative colitis The exact dosage remains to be determined and be individualized for each patient.—*Editor*

is that the benefit which may be produced by the use of so called disinfecting irrigations is offset by the irritation they cause It is essential to remember that no matter what the disinfectant may be one cannot hope by giving it as an enema to eradicate the infection The disease extends deeply through all the layers of the bowel and at times into the mesentery and even into the blood stream Consequently the most that can be accomplished by intestinal irrigation is cleansing of the surface and that only for a few minutes In cases in which there is much perianal infection as there is in cases in which a fistula is present irrigation of the rectum with warm physiologic salt solution has made the patients comfortable In the few cases in which such irrigations seem indicated physiologic salt solution is as useful as solutions of silver nitrate mild silver protein acriflavine or any of the many other drugs that have been used for this purpose

In the case of a massive hemorrhage 3 to 4 oz (90 to 120 gm) of starch mixed with warm water and made into a thick paste so that it just flows and can be instilled into the rectum has been known to stop such a hemorrhage One grain (0 065 gm) of powdered opium may be added to the suspension

Removal of Foci of Infection Foci of infection should be removed if possible for they may serve as depots from which infection of the bowel may arise If one wishes to do everything possible one should remove teeth that have periapical abscesses and suspicious looking or definitely infected tonsils The tender and inflamed rectal wall usually will prevent the massage necessary to clear up prostatitis Perianal infections cryptitis and papillitis should be treated cautiously In general it can be said that foci of infection should be removed in the stage of remission or at least in the quiescent stage of the disease

Parenteral Administration of Fluids Since the patients frequently are seriously ill it is often necessary to administer fluids parenterally The solutions used are (1) physiologic solution of sodium chloride 9 gm of sodium chloride per liter (2) Ringer s solution 9 gm of sodium chloride 0 24 gm of calcium chloride 0 42 gm of potassium chloride 0 20 gm of sodium bicarbonate in 1000 cc of triple distilled water (3) duodenal replacement formula (D R) 7 0 gm of sodium chloride 0 90 gm of potassium chlo-

[illegible]

sodium lactate 12 0 gm of sodium chloride 0 8 gm of potassium chloride 0 4 gm of calcium chloride in 2 liters of water The main constituent of all of these solutions is sodium chloride in a concentration which is isotonic or slightly hypotonic when compared with the concentration in the blood The last three solutions contain other ions which are helpful but perhaps of secondary importance Two other solutions used for parenteral administration are a 5 or 10 per cent solution of dextrose in distilled water or in physiologic solution of sodium chloride

The indications for parenteral administration of fluids are (1) dehydration (2) maintenance of water balance mineral balance

logic solution of sodium chloride over and above that needed to replace abnormal loss of fluid should be given in 24 hours In cases of severe chronic ulcerative colitis in which the value for the plasma protein is low even this amount is excessive since that extra sodium chloride tends to produce edema rather than to correct the acidosis or alkalosis

Surgical Treatment The problem of when operation should be performed arises often when one is dealing with this disease There was a time when operation was thought desirable whenever the patient did not respond promptly to medical care As a result of this opinion in many cases of the fulminating form of ulcerative colitis intestinal stomas were established in the hope that drainage of the fecal contents through the abdominal wall away from the diseased segment of bowel might allay the activity of the disease and permit healing The high mortality rate accompanying surgical intervention has discouraged operation for this phase of the disease

Intractability has been considered a definite indication for an abdominal intestinal stoma Men of considerable surgical experience postulated that this infectious process

reached a stage at which the changes were irreversible and that when the disease reached this stage an intestinal stoma or perhaps even colectomy was indicated In some instances this was probably true but I have not been able to find the man who can even approach an expression of the time when a disease process has become irre versible

There is however a group of lesions which are inclined to occur as late sequelae of the disease and which definitely are surgi cal problems The principal ones are polypo sis neoplasms strictures extensive perianal fistulas localized perforation and abscesses of one kind or another Except for these com plications and for acute intercurrent surgical disease surgical treatment should be used sparingly

The hope has recurred frequently that cure of this disease might be obtained by deflecting the current of intestinal content out of the abdomen Various methods of doing this were tried Ileostomy was found to be the procedure of choice When ileos tomy becomes necessary for complications it is usually performed when the patient s condition has become generally satisfactory Then it can be performed with reasonable safety Ileostomy has been employed in about 5 5 per cent of the total number of cases of thrombo ulcerative colitis in which the patients have been treated at the Mayo Clinic

Cattell has put the problem of some of the patients suffering from this disease aptly when he said that "ileostomy is the price that some patients must pay for life al though he considered the disease primarily a medical problem

It becomes obvious that when the disease has reached the stage at which ileostomy is advisable colectomy should be performed at a later date but as soon as the patient s con dition warrants Usually it is well to post pone colectomy for at least 6 or 8 weeks after ileostomy has been performed

These observations lead one to the inevi table conclusion that if and when thrombo ulcerative colitis has reached the stage at which operation seems indicated ileostomy and subsequent colectomy would seem to be the procedures of choice Only occasionally will healing subsequent to ileostomy be such as to warrant later closure of the stoma However it must never be forgotten that after ileostomy medical management should proceed in the manner employed before the operation was performed If this is done carefully there will be a few cases in which the stoma can be closed reasonably safely later on

In only a few cases has it been possible to close an iliac stoma once made for this form of chronic ulcerative colitis From his observations the writer can say that such stoma probably was established when the disease was not very extensive When a stoma once has been established in cases of this disease it generally can be considered a permanent affair and colectomy will be come advisable as a subsequent surgical procedure

With the current wave of enthusiasm con cerning vagotomy for peptic ulcer it was natural that this operation would be tried for the control of the diarrhea of ulcerative colitis The thought was advanced that a severance of the vagus nerve would inter fere with the gastro ileal reflex In a few patients with mild forms of ulcerative colitis this has been so Whether this justifies an operation of such magnitude will be for the future investigators and students of the problem to decide Vagotomy has not been helpful when ulcerative colitis has reached a fairly advanced stage in fact in some patients of this type who were vagotomized there occurred a great increase in bowel activity and an intractable diarrhea resulted

Prognosis —Although the present treat ment of thrombo ulcerative colitis leaves much to be desired a distinct advance has been made over other previous and contem porary endeavors Thrombo ulcerative colitis must be considered somewhat as tuberculosis is considered namely as a regressive de-structive inflammation of the large intestine in which to stem the tide many measures must be brought into play and the patient as well as the physician must learn to under go long suffering and to have patience

The life span of patients who have thrombo ulcerative colitis may be materially shortened by the ravages of the disease The experiences related in previous paragraphs clearly indicate how devastating this malady can be and how it can relegate a healthy

robust person slowly or relatively quickly to chronic invalidism and intense suffering They also reveal that by careful continuous management a person so condemned can be restored to normal health and usefulness and they suggest that once a patient has had this disease he may have to adapt his future mode of living for years to restrictions im posed on him by the fact that he is a po tential colitis patient

Factors such as infection of the upper part of the respiratory tract physical fatigue marked nervous fatigue and anxiety states have been found to predispose to the dis ease similar factors may initiate relapses once the condition has been controlled

It has been found that with the passing of time more and more patients are making a satisfactory recovery and are being re stored to a useful life

Although the results are not so striking in the fulminating type of the disease as they are in other types even here great progress has been made and whereas only a few years ago nearly all the patients who had this type of the disease succumbed now most of these patients are saved and once their symptoms are controlled the patients usually remain well

The question might well be asked "What type of person can best withstand the dis ease and at what age do patients tolerate the disease best? Here an apparent paradox exists Children who are less than 12 years of age withstand the disease poorly and the percentage of such children who recover after the disease has caused much damage is relatively small Although the disease is particularly devastating when it occurs in childhood this does not preclude the living of a normal span of life by a child so afflicted and my experience indicates that when a patient has survived the first years of the onslaught of the disease the tendency in general is that the disease becomes milder or perhaps the patient becomes progressively better able to tolerate the condition On the other hand if the disease begins when the patient has passed the age of 60 years the proportion of recovery is the greatest and approaches 100 per cent As in most severe chronic infections however the onset is com monly in the second and third decades of life These patients usually are extremely ill yet the high percentage of satisfactory re coveries among them illustrates that unre lenting effort to control the disease is worth while Once the patients have recovered and remain free of relapses their longevity should not be affected by the fact that they have had the disease

In that group of patients in which the onset is insidious and even among those cases in which the disease is severe from the onset the tendency is for the first attack to be mild and of short duration for the second attack to be less mild and of longer duration and for the next attack to be more severe and more intractable with remissions between attacks becoming shorter and shorter until the patient is in continuous trouble Furthermore after an adequate program of management has been estab lished remissions become longer and ex acerbations become progressively less severe and of shorter duration if they occur at all until finally the patient remains free of symptoms This thought must be impressed on the patient so that he may not become discouraged and will follow an established program without interruption and without trying to take short cuts What has been said here can be said about the patient for whom ileostomy becomes advisable

It should be remembered that even though the active symptoms of the disease may have subsided a patient must not relax his vigi lance If vigilance is maintained results may be excellent Again it may be said that there is analogy between the course of this disease and that of tuberculosis and every patient who has had a severe attack of ulcera tive colitis is a potential colitis patient Re lapses are common if these matters are not borne in mind The most common causes of relapse are (1) infection of the upper part of the respiratory tract (2) mental and physical trauma and (3) the lighting up of distant foci of infection

J Arnold Bargen

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REGIONAL (SEGMENTAL) ULCERATIVE COLITIS

The regional form of ulcerative colitis is one of the least common varieties Various authorities have found that it comprises between 3 and 5 per cent of any large series of cases of ulcerative colitis It presents the most bizarre picture has the least clear cut manifestations and offers the greatest diagnostic difficulties of any of the various types of colitis

No common etiologic agent has been found for regional ulcerative colitis One could think of this form as the problem child of colitis and if as some insist the term "non specific is to be applied to some forms of ulcerative colitis it could be applied to this one In this form of colitis more than in any other we depend on the roentgenologic examination of the large intestine

Treatment It has been accepted generally that resection of the diseased segment of the bowel is the preferred treatment of regional ulcerative colitis However when to operate and which patients may be restored by medical measures remain unsettled problems

One can say with a great degree of certainty when not to operate It is unwise to explore the abdomens of these patients during the acute stage of the disease Attempts at resection at that time are fraught with unnecessary risk However it is well to place the patient at rest in bed and provide all the supportive treatment available Intravenously administered fluids blood transfusions low residue diets and the judicious administration of sulfonamides have helped many a patient through the active stage of the disease Sulfasuxidine and sulfathaladine have been particularly efficacious the latter being the drug of choice 120 to 130 grains (8 to 12 gm) are administered daily in divided doses Furthermore, such complete relief of symptoms frequently has been achieved by these supportive measures that resection was later deemed unnecessary We can now say that many of these patients respond to medical measures

If however, so much damage to the intestinal wall has occurred that there is a severe persistent deformity as depicted by roentgenologic study resection is inevitable Relief of this condition may be accomplished by exteriorization of the involved portion of the colon or by colocolostomy, or ileocolostomy, and subsequent resection

A well ordered program of preoperative care is of greatest value in these cases This may result in a recession of acute symptoms and the patient s ability to withstand surgery may be immeasurably improved Sulfasuxidine administered in divided doses to total 240 grains (16 gm) the first day and at the rate of 60 grains (4 gm) every 4 hours for 4 to 6 days before surgery or sulfathaladine at the rate of 120 grains (8 gm) in divided doses during each 24 hour period has been most helpful In some cases the addition of streptomycin has been indicated By and large the sulfonamides represent the preoperative drugs of choice however occasionally a patient s sensitivity to these drugs forbids their use and in these cases and for some of the more seriously ill patients streptomycin is particularly helpful About 2 gm of the latter should be given in divided doses each 24 hours * Saline aperients and cleansing enemas should also be given until the day of surgery so that the intestine is well cleaned before surgery is undertaken A residue free diet especially high in carbohydrate is helpful in preoperative care

Complications The major complication in these cases is colonic perforation This may necessitate temporary colostomy proxi

allow several months to intervene between several stages of this procedure Other complications common to thrombo ulcerative colitis have been encountered in this disease as well principally those in which there

* Chloromycetin and aureomycin may prove to be of value in regional ulcerative colit s Specific information as to their effecti eness in this condit on is not available at the time of this writing —*Ed tor*

were systemic manifestations, that is, arthritis erythema nodosum, neuritis, infection of the urinary tract, phlebitis and deficiency states late in progressive infection Stricture of the bowel has occurred, hemorrhage has occurred rarely but perirectal abscess fairly frequently Since most of these complications demand individual attention, it would be difficult to lay down rules for the treatment of any one of them It should be emphasized, however, that if perirectal abscess occurs in the presence of diarrhea, it is important that careful investigation of the intestine above the rectum be carried out Disease in the intestine proximal to the rectum should be controlled before operation on perirectal infections and fistulas, except in cases in which it is necessary to operate immediately, as for drainage of an abscess or to institute measures for control of anal discomfort

J Arnold Bargen

FUNCTIONAL DISORDERS OF THE COLON

Physiologic Principles Functional disorders of the colon are characterized physiologically by hyperirritability of the neuromuscular mechanism of the bowel resulting from local mechanical or chemical irritation or from excessive stimulation of the autonomic nervous system The dysfunction of the colon may consist of hypertonicity with irregular and intermittent spasm hyperperistalsis or both The abnormal muscular contraction localized distention and increased smooth muscle tension of the bowel lower the threshold for visceral pain and thus cause abdominal distress of varying type and severity *The disturbed motility* of the colon interferes with the normal rate of progress of fecal material, resulting in either constipation or diarrhea In order to treat these patients satisfactorily, it is necessary to keep firmly in mind certain fundamental physiologic principles and not to be misled by the varying notions regarding bowel function so common among the laity Gastric emptying takes place in a rather uniform time, one to 7 hours depending on the size of the meal The transit of food through the small intestine, where digestion takes place, also occurs in a rather constant time, 2 to 4 hours In the colon, however, the rate of travel is much slower and more variable, the transit time ranging from a few hours to several days The essential function of the colon is not digestion, but the absorption of water and the condensation of the watery small intestinal content into a formed stool for infrequent convenient evacuation The desire to defecate is a conditioned reflex induced by the passage of fecal material from the descending colon and sigmoid into the rectum, by sitting on the toilet, by eating a meal (the gastrocolic reflex), by smoking a cigarette, or in various other ways

Normal defecation consists of a well formed collection of feces, an inch or so in diameter, several inches in length, and firm in consistency The spasticity of the irritable colon may induce prolonged retention of fecal material excessive quantities of water may be absorbed and the feces evacuated as hard dry balls or as narrow, ribbon like masses Constipation may result also from atony of the bowel and insufficient muscular activity, as in debilitated or elderly individuals but this type of constipation is not ordinarily accompanied by abdominal pain Consequently, the passage of hard dry feces especially in the presence of abdominal distress usually signifies excessive spasm and too much irritation rather than too little Soft unformed watery evacuations are indicative of hyperperistalsis, the feces traversing the colon too rapidly to permit the normal absorption of water

The presence of excessive amounts of mucus is of some significance for mucus is secreted through the digestive tract in response to irritation, the more pronounced the irritation, the more mucus in the feces

The etiologic factors in functional disorders of the colon are of two general types (1) physiologic, direct stimulation of the neuromuscular mechanism of the bowel by mechanical or chemical irritants, and (2) emotional or psychologic, mediated by the autonomic nervous system The physiologic causes include the immoderate consumption of irritating and laxative foods excessive smoking, and the habitual use of laxatives, cathartics or enemas The emotional or psychologic components seem usually to arise from the many small continued anxieties and frustrations of life, rather than from specific precipitating events, although in some cases

a direct cause and effect relationship may be apparent Bad childhood habit patterns, emotional and intestinal, are often present and seem to result in a "conditioning" or "sensitization" of the colon The disordered function of the bowel may thus be attributed to a hypersensitive neuromuscular mechanism, resulting from emotional stress, bad habit patterns, and similar nervous factors, plus the physiologic irritation of cathartics, enemas, highly laxative foods, and other poorly tolerated dietary practices

Treatment Treatment requires an accurate appraisal of the physiologic factors involved and careful evaluation of the patient as an individual While the specific procedures employed should be adjusted to the requirements of each patient, certain principles are almost invariably applicable

Reassurance It is important initially to relieve the patient's anxiety concerning the possible presence of serious organic disease This is accomplished most effectively by a thorough investigation comprising a careful history, complete physical examination, including digital examination of the rectum proctosigmoidoscopy, blood count urine analysis, examination of the feces for occult blood and parasites and roentgen examination of the digestive tract The manner of informing the patient of the results of the study is of some consequence It should be done with a calm, firm, cheerful, and secure attitude, not with too much pomp and circumstance, nor with great levity and casualness The examination is of great concern to the patient, he should be reassured rather than frightened or belittled The verdict of "no organic disease" must be followed by some explanation of the mechanism of the distress Injunctions to "forget it, it is all in your head," etc, are ineffective, they constitute poor psychotherapy and poor medicine Terminology is of some importance in this respect for the various names may have specific connotations for different patients "Colitis" is often confused with ulcerative colitis "Mucous colitis" may be regarded as an inflammatory disease of the bowel "Spastic colitis" may be envisioned as an intense intractable spasm "Nervous indigestion" may be interpreted as tantamount to an imaginary disease or a disturbed mind The patient should be reassured that while irritability of the colon is a common cause of abdominal distress, it does not lead to serious consequences This form of superficial psychotherapy usually suffices, occasionally, a more complete analysis of the patient and his problems by a trained psychiatrist is required

Rest and Exercise Rest is of definite value, although the amount required depends on the severity of the disturbance and the circumstances present In the average patient, long hours of sleep at night and a rest period during the afternoon are adequate Some individuals benefit greatly from a vacation away from home and the problems of their daily routine Patients with severe abdominal pain may require complete bed rest in the hospital for a period of several weeks On the other hand, in some individuals exercise is helpful it should not be too strenuous and it should provide pleasure

Heat to Abdomen In most instances, the application of heat to the abdomen in the form of an electric pad or a hot water bottle seems to quiet the hyperactivity, reduce the flatulence, and relieve the abdominal discomfort Heat may be applied continuously, or on alternate hours, or for an hour or two after each meal, depending upon the severity of the distress A hot bath, preferably in a tub, is often helpful

Antispasmodics and Sedatives The drugs of greatest value are the antispasmodics and sedatives Tincture of belladonna, a time-honored remedy, may be prescribed in doses of 10 or 15 drops (0 6 to 1 0 cc) three or four times daily Atropine sulfate, $\frac{1}{120}$ or $\frac{1}{150}$ grain (0 0005 or 0 0004 gm) may be given by mouth three or four times daily, or $\frac{1}{60}$ grain (0 001 gm) may be administered [illegible]

[illegible] and to produce fewer side effects, appear to be of questionable superiority

Barbiturates promote rest and sleep, relieve anxiety, and decrease intestinal hyperactivity Phenobarbital in doses of 0 015 or 0 03 gm may be given three or four times each day An effective prescription combines in tablet form phenobarbital 0 03 gm and extract of belladonna 0 0075 gm When insomnia exists, the phenobarbital may be given in a single dose of 0 1 gm at bedtime

Other preparations such as seconal (0 1 gm) or occasionally chloral hydrate (1 to 2 gm) may be substituted if preferred Bromides may provide equally satisfactory relaxation but their use should not be prolonged because of the hazards of bromoderma or bromidism Opiates are rarely needed and they are not desirable because they increase the tonicity of the bowel and also because of the danger of addiction However codeine sulfate 0 03 or 0 06 gm may be used occasionally for the relief of severe intestinal distress

REGULATION OF INTESTINAL FUNCTION Patients should be educated to obtain satisfactory bowel movements spontaneously Laxative preparations of all kinds including mineral oil cathartics and large enemas are to be avoided They increase the tendency to colonic spasm and pain and are unnecessary This is true also of the relatively mild so called bulk producing substances although in general these are much less disturbing than the chemical laxatives The elapse of several days or more without a bowel movement is of no consequence *provided* fecal material is not accumulating in the rectum Most patients will recognize this sensation and will so inform the physician The majority of patients will be alarmed at the passage of time without defecation and will ask for a laxative The request should be denied and reassurance given but the rectum should be examined daily to make certain that a fecal impaction is not developing in the rectum It is rare for impactions to form above the rectosigmoid Oil enemas may be given prophylactically when there has been no defecation during the entire day or when the stool has been hard and dry Three or 4 oz of warm olive oil or mineral oil are instilled into the rectum by means of a rubber bulb type of ear syringe or by means of a small funnel and a large male catheter The retention enemas may not be necessary or desirable but it is important to be on the alert for the development of such impactions If a fecal impaction develops it should be broken up digitally and removed or evacuated by large enemas of tap water Oil enemas are of no value for this purpose

Laxatives and cathartics need not be prohibited under all conditions Many patients especially elderly persons for one reason or another develop the cathartic habit experience no distress or ill effects therefrom and may be permitted to continue the regimen they have found effective

The act of defecation can be inhibited by neglect of the normal urge The rectum gradually adapts itself to the bulk of feces and in time the desire to defecate may be lost completely The importance of regular habits therefore should be emphasized

may be used to stimulate the defecatory reflex when it is lacking and when the stool tends to collect in hard masses in the rectum Glycerin suppositories also will be found effective for this purpose in many individuals

Constipation may be further aggravated by anal spasm resulting from fissures or hemorrhoids these conditions should be treated by appropriate measures

DIET The dietary management is based on the varying laxative qualities of different foods (Table I) All food and drink is more or less stimulating to the digestive tract there are however marked differences quantitative and qualitative mechanical and chemical in the effects of various foods The usual patient is best managed by prescribing a diet estimated to give the laxative effect required It should produce firm formed stools rather than hard stools or on the other hand soft or liquid stools A diet sheet should be supplied with specific instructions as to the foods to be eaten and those to be avoided In practice a diet form such as the one outlined may be used it enables the physician to delete easily certain foods or groups of foods Since the abdominal distress and constipation are attributable to spasticity of the colon the more irritating items in Sections 5 6 and 7 of the diet are prohibited entirely A fairly satisfactory procedure is that of permitting the patient to eat all of the foods in Sections 1 to 4 inclusive except for the more laxative cooked fruits and vegetables The amount of cooked fruit and vegetable should be stipulated as perhaps two liberal (3 to 4 oz) servings of each daily If the symptoms subside qualitative and quantitative additions to the diet

may be made If the feces are hard and dry the intake of cooked fruit and vegetable is increased to three servings of each daily in patients with constipation and without abdominal distress the diet may be augmented by the addition of such foods as lettuce celery and ripe tomatoes The regimen is continued for several weeks or months or even longer if necessary Indeed the majority of patients find it desirable to maintain some form of dietary restriction in definitely

The treatment of patients with diarrhea of functional origin is similar Rest in bed the application of heat to the abdomen and the use of phenobarbital and belladonna are helpful Codeine (30 mg) may be given hypodermically together with 0 4 mg of atropine when severe pain is present Paregoric bismuth and similar preparations are of little value and indeed may aggravate the distress by increasing the tonicity of the bowel In acute disturbances with severe diarrhea it may be desirable to omit all food for 24 hours and to administer 5 per cent glucose in isotonic saline solution intravenously The first substances to be given should be hot water broth barley gruel and weak tea followed by oven toasted bread cream of wheat boiled milk cooked eggs rice custard and jello (Section 1 of diet) The diet is gradually expanded as improvement occurs Excessively hot or cold foods should be avoided Fruits and vegetables both cooked and raw are prohibited until the diarrhea has subsided and the stools are formed The diet should be continued until the bowel function has been normal for several weeks

There is usually no difficulty in selecting a menu adequate in nutritional requirements except in those patients with acute bowel distress who are able to tolerate only the foods listed in Section I However this restricted diet may be safely taken for the several days necessary for the acute symptoms to subside The use of vitamins though unnecessary may be permitted

Failure with the therapeutic program described is usually attributable either to an unrecognized organic disease or a difficult unsolved psychiatric problem In most instances the skillful application of the principles outlined brings to the co-operative patient restoration of normal bowel function and a gratifying relief of symptoms *

TABLE I

LAXATIVE EFFECT OF VARIOUS FOODS

(1) *Foods with Minimal Laxative Effect and Hence Best Tolerated in Acute Disturbances*
   Water weak tea rice or barley gruel meat broth cream of wheat farina o en toasted bread zwieback toasted soda crackers with butter soft cooked eggs boiled milk custard, plain jello

(2) *Most Substantial But Relat vely Bland and Easily Digest ble Foods*
   Cereals with milk or cream refined rice rice krispies puffed rice puffed wheat corn flakes oatmeal (well cooked)
   Soups consomme strained chicken broth strained vegetable strained cream of rice strained cream of potato strained cream of celery stra ned cream of mushroom cream of tomato
   Cheese cream American Swiss cottage
   Fish salmon tuna whitefish
   Fowl chicken turkey squab
   Meats beef veal lamb ham liver (broiled bo led roasted or baked)
   M scellaneous crisp bacon macaroni noodles spaghetti vermicelli
   Potato baked mashed au gratin or escalloped
   Breads wh te toast croutons bread sticks milk toast
   Milk products milk cream butter
   Other beverages tea coffee postum
   Desserts custards vanilla caramel r ce puddings bread tapioca cornstarch cottage snow
   cakes angel food icebox plain sponge
   cookies arrowroot hydrox Peter Pan vanilla wafers
   pies lemon cream custard banana cream

(3) *Cooked or Canned Vegetables More Laxative Chiefly because of Greater Residue*
   (a) Moderately irr tating asparagus string beans carrots spinach sweet potatoes peas beets tomatoes squash

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* Methylcellulose has been ad ocated by Bargen

[illegible] usual dose is 4 tabl ts before each meal and at bedtime —*Ed tor*

Bargen J A A Method of Improving Function of Bowel The Use of Methylcellulose *Gastroenterology* 13 275 1949

(b) More irritating artichokes parsnips onions cabbage cauliflower rutabaga eggplant green peppers turnips kohlrabi broccoli navy beans lima beans corn

(4) *Cooked or Canned Fruit More Laxative because of Chemical Irritants*

(a) Prunes peaches applesauce apricots pears baked apple cherries

(b) Figs plums dark cherries berries grapes pineapple rhubarb

(5) *Raw Vegetables More Laxative*

Lettuce tomato celery watercress endive radishes onions cucumbers cabbage

(6) *Raw Fruits More Laxative*

Banana (least laxative) oranges (juice sections whole) grapefruit apples melon pineapple berries of all kinds pears peaches cherries grapes plums apricots avocado pear

(7) *Miscellaneous Foods Some Very Laxative such as Honey and Beer*

Icecream with fruit or nuts syrup molasses honey popcorn candy nuts pickles olives relishes catchup spices various seasonings buttermilk French fried potatoes raisin bread soft or carbonated drinks coca cola ginger ale sodas cider

Alcoholic beverages beer whiskey wine etc

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DIVERTICULOSIS AND DIVERTICULITIS

The formation of diverticula cannot be prevented nor can diverticula be made to disappear While diverticulosis per se does not cause symptoms and therefore requires no treatment it is often accompanied by irritability of the colon and alleged constipation The treatment is the same as that outlined for functional disorders of the bowel Laxatives cathartics and enemas are irritating and should not be used routinely In some patients small amounts of mineral oil (15 to 30 cc) given by mouth are well tolerated but in others the symptoms are aggravated The rectal instillation of 3 or 4 oz of warm mineral oil or olive oil facilitates the elimination of hard dry feces Tincture of belladonna 10 to 15 drops or atropine sulfate 0 0005 to 0 0004 gm may be prescribed before meals and in the evening Phenobarbital in doses of 0 03 gm may be *given four times daily*

Diverticulitis most often involves the sigmoid or descending colon because of the higher incidence of diverticulosis in this region and the smaller caliber of the bowel The formation within the diverticula of small hard fecal masses may serve as foreign bodies and precipitate an infection Acute diverticulitis in the majority of instances responds to conservative treatment including rest in bed the application of heat to the abdomen and the avoidance of laxatives and enemas The diet initially may be limited to warm liquids or soft fo

larged as

vomiting

hold food by mouth for several days and to administer 5 per cent glucose in isotonic saline solution intravenously Mineral oil softens the stool facilitates its evacuation and may be given by mouth in daily quantities of 30 to 60 cc retention enemas of mineral oil or olive oil are similarly helpful Sulfasuxidine 2 gm every 4 to 6 hours may help to control infection within the lumen of the bowel If high fever and marked leukocytosis are present the administration of 30 000 to 50 000 units of penicillin every 4 hours may be necessary One or 2 gm of dihydrostreptomycin every 24 hours may aid in controlling an infection that is not responsive to penicillin Aureomycin or chloromycetin 250 to 750 mg every 6 hours may prove to be valuable agents in patients with severe infections

Obstruction may occur as the result of inflammatory edema and fibrosis Conserva

effective

than it is in obstruction of the small intestin nevertheless may be utilized for decompression of the bowel Persistent obstruction may

necessitate the establishment of a colostomy in the transverse colon or the cecum With the fecal current thus diverted the diverticulitis and the obstruction in some cases subside completely or at least sufficiently to permit resection of the diseased segment of the intestine

Diverticulitis may progress to acute perforation with local peritonitis, chronic perforation with the formation of a peridiverticular abscess or rarely spontaneous rupture of an inflamed diverticulum into the free peritoneal cavity Acute perforation of course requires immediate operation the procedure after the abdomen has been opened will depend on the findings and the preference of the surgeon

Chronic perforation with the formation of an abscess is except for chronic obstruction the most common complication of diverticulitis Conservative nonoperative treatment with chemotherapeutic agents antibiotics and other supportive measures may be attempted for several days in the hope that the abscess will resolve spontaneously In the majority of cases it is necessary to incise and drain the abscess and to establish a colostomy More radical surgery should not be undertaken at this time because of the danger of extension of the infection and because of the technical problems involved in dealing with inflamed and edematous tissues

Perforation may occur into adjacent loops of bowel the urinary bladder or the abdominal wall and result in the formation of permanent fistulas The treatment is surgical and consists initially of a transverse colostomy or a cecostomy diversion of the fecal current is particularly important in dealing with a vesicocolic fistula to avoid the serious complication of an ascending infection of the urinary tract. More definitive therapy may be undertaken after an interval of several weeks or months, the fistula and the involved segment of a bowel are resected with end to end anastomosis and closure of the secondary openings of the fistulous tract A further indication for resection is the inability to differentiate conclusively between diverticulitis and neoplasm

Careful preoperative and postoperative treatment are necessary to reduce the operative morbidity and mortality to a minimum The oral administration of sulfonamide drugs or streptomycin for several days before operation reduces the bacterial flora of the gut and lessens the possibility of serious infection The principles of postoperative care are those of intestinal surgery in general gastric suction administration of antibiotics and fluids the maintenance of nutrition and early ambulation

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DISEASES OF THE LIVER AND BILIARY TRACT

TOXIC HEPATITIS

poisoning etc) or may complicate other illnesses (pneumonia septicemias yellow fever, syphilis amebiasis malaria dengue infectious mononucleosis etc)

Treatment Treatment consists of the following general measures

Bed rest is most important The patient should be kept at strict bed rest usually for 3 to 4 weeks or for one week after the following requirements have been satisfied return of the liver to normal size (or if slightly enlarged it should be nontender and there should be an absence of symptoms), icteric index below 20 units and the total serum

bilirubin below 2.5 mg per cent, and the bromsulfalein retention below 10 per cent in one hour (5 mg per kilogram dose). Return of symptoms, enlargement of the liver, or tenderness over the liver area in a patient who has become ambulant necessitates prompt return to bed rest.

DIET. The diet is as important as bed rest and should be high in protein (125 to 200 gm), and carbohydrate (300 to 400 gm) and moderate in fat (80 to 90 gm). High protein liquid feedings have been valuable in our experience to supplement the regular diet and also in patients who will not take solid foods. One of these may be made by adding 8 eggs, 4 oz. of skimmed milk powder, and 6 oz. of lactose to 1 qt. of skimmed milk and flavoring to taste. Such a mixture will furnish 350 calories (C = 49 gm, P = 20 gm, F = 8 gm) per glass (240 cc). One hundred gm. of protein hydrolysate (vipeptolac—Wyeth, essenamine—Winthrop Stearns, ledinac—Lederle, etc.) may be substituted for the eggs and milk powder in the mixture above although usually they are less palatable and more expensive.

For patients unable to take adequate oral nourishment, tube feeding may be resorted to. If this is not possible, protein hydrolysates in glucose (amigen—Mead Johnson, parenamine—Winthrop Stearns, hyprotigen—Baxter) may be administered intravenously (2 or 3 liters daily will furnish 100 to 150 gm. of protein hydrolysate). A normal diet may be resumed as the patient recovers and the jaundice subsides.

Fluid intake should equal 2400 to 2800 cc daily, except where there is oliguria, anuria or marked ascites. In such cases, fluids must be balanced with great caution to prevent overhydration or dehydration and as a general rule, to a basal level of 1200 to 1500 cc one may add an amount equal to the urinary output for the previous 24 hours to determine the total permitted. Fluids administered may be 5 per cent glucose in physiologic saline, especially if vomiting or acidosis is prominent, protein hydrolysates (for nutrition), irradiated plasma, concentrated human serum albumin, or whole blood (for nutrition, dehydration and to combat shock). Where blood or plasma has been used, it might be wise to administer 10 cc of gamma globulin at monthly intervals for two or three doses in an attempt to prevent homologous serum hepatitis.

Supplemental vitamin therapy may be given orally and parenterally and should furnish adequate amounts of vitamin A (5000 U.S.P. units daily), vitamin C (100 mg daily) and B complex (thiamine chloride 5 mg daily, riboflavin 4 mg daily, niacin or niacin amide 30 to 50 mg daily). Vitamin P (rutin) in doses of 50 to 300 mg daily may be given for purpura resulting from a deficiency of this vitamin. Vitamin K may [illegible] cubic centimeter) in doses of 3 to 5 cc three weekly is a definite aid. Along these lines intraheptol (Lederle), an aqueous liver extract given intravenously, may be used as an adjunctive measure. Testosterone in doses of 25 to 100 mg three times weekly has been said to result in clinical improvement.

Oxygen is often used to combat cyanosis and anoxia, and we have employed antibiotics prophylactically to prevent pneumonia in very ill patients. For more intensive therapy of the acidosis that at times develops, the reader is referred to the section of [illegible] recovery in these cases. Management of ascites is discussed in the section on therapy of cirrhosis of the liver.

Specific forms of therapy may include (1) Removal of any hepatotoxic agents including those that may have precipitated the illness or contributed to it; where the toxic hepatitis is secondary to some other infection, appropriate antibiotic therapy should be instituted (penicillin for pneumonia and syphilis, emetine and diodoquin for amebic [illegible]

gm daily) should be employed where there is reason to suspect that fatty metamorphosis of the liver may be present (carbon tetrachloride and chloroform toxicity). In addition there is some evidence that choline may be more beneficial than methionine and that it may even be helpful where fatty infiltration is not demonstrable, (3) BAL (2,3

limercaptopropanol) may be utilized where he toxic hepatitis is a result of arsenic or nercury poisoning This drug is given in loses of 2 5 to 3.0 mg per kilogram body veight every 4 hours the larger dose being mployed in the more seriously poisoned patient Six injections of this dosage are given on the first 2 days of treatment four on the hird day and two injections daily from the ourth through the 10th days

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ACUTE YELLOW ATROPHY OF THE LIVER

The results of therapy in acute yellow atrophy or acute diffuse necrosis of the liver as it is now known are disclosed by the fact that an essential point in the diagnosis of true acute atrophy of the liver is its fatal outcome (Lichtman) However, a substantial number of these cases has been reported in the literature wherein recovery was claimed following treatment Many observers have asserted that such cases were actually subacute yellow atrophy of the liver or sub acute diffuse liver necrosis and not true cases of acute liver atrophy Since the same factors operate in both the acute and sub acute varieties and the difference is only in the degree of liver involvement the treatment for both varieties is described

Treatment of this disease requires heroic

is through the intravenous route If the patient is able to take oral food or fluids at least 500 gm daily should be taken by mouth Since most patients are too sick for this the *intravenous administration of 10 per cent* glucose should be given slowly at the rate of 250 cc per hour a total intake of 3000 cc will thus insure the intake of 300 gm of glucose or 1200 calories In this way the urgent need by the liver for a sufficient supply of glucogen is met and the means provided for preventing the fatal hypoglycemia which may occur in these patients (Bockus) The total glucose intake 1000 cc should be in normal saline to insure adequate sodium balance Next or equal in importance is the intravenous administration of protein Probably the most efficient way of accomplishing this is through whole plasma in large amounts *since the hepatic necrosis renders* proper utilization of amino acids difficult Irradiated plasma is preferable to reduce the danger of subsequent development of homologous serum hepatitis

Intravenous methionine in 5 per cent solution has been reported of value in stimulating regeneration in these cases (Tumen) A 10 per cent solution in distilled water (500 cc) may be administered simultaneously with the intravenous glucose solution

Vitamin B complex and vitamin K should also be given together with the above stated intravenous infusions At least 50 to 100 mg of thiamine hydrochloride and 250 to 500 mg of nicotinamide should be incorporated in the intravenous therapy daily (Snell and Butt) Serious depletion of prothrombin usually is present 10 mg of vitamin K should therefore be tried and included in the daily intravenous infusions Unfortu

prothrombin Hemorrhagic tendencies are therefore best combated by transfusions of whole blood (500 cc) until the blood prothrombin time approaches normalcy

Anemia is controlled by blood transfusions, if the anemia produces anoxemia this is best treated by the use of oxygen by an oxygen tent or through a BLB mask Restlessness is most safely treated by the soluble barbiturates rather than by opiates which rely on the liver for detoxification

In the writer s experience pruritus may be controlled in about one third of the cases by the use of ergotamine tartrate, 1 mg three times daily by mouth, or subcutaneously once daily in from 1 to 3 mg dosage This drug however, can be toxic and must be observed carefully Rowntree found calomel useful in 1 5 to 3 mg dosage once every hour for four doses per day, without a saline purge for several days In completely intractable cases Wilbur has reported the successful use of intravenous procaine hydrochloride in dosage of 20 cc of 0 1 per cent solution, administered slowly

Hepatic coma has been reported as successfully treated in some cases by the daily intravenous administration of 5 gm lactic acid in 100 cc of normal saline solution (Eppinger)

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PORTAL CIRRHOSIS OF THE LIVER

Cirrhosis of the liver is no longer regarded as a hopeless, incurable disease which progresses unchecked until death intervenes. Recently numerous reports have demonstrated that many patients with hepatic cirrhosis can improve or even recover as determined by clinical observations and laboratory tests following treatment to be described below The writer has reported a detailed analysis of the results of treatment of cirrhosis under controlled conditions in a series of some 100 patients studied over a 10 year period, the results of these studies revealed that an encouraging and growing number of patients had improved or recovered to the point where they were able to resume their work or household activities

The patient should be kept in bed at complete rest for several weeks until the acute phases of the disease have passed and substantial improvement has taken place

Diet The diet is one of high protein, high carbohydrate, and low fat content The daily maximal protein intake aimed at is approximately 200 gm, carbohydrate from 300 to 500 gm, and fat 50 to 75 gm in those patients able to take a full solid diet In the severely decompensated patient for whom a liquid diet is required, the caloric intake is necessarily low, but is increased to maximal tolerance as soon as possible Lean meat is eaten at least twice daily, skimmed milk and cottage cheese are taken in liberal quantities

Lipotropic Agents (Preventive of Fat Deposit) Choline Choline in the salt form is administered, 6 gm, preferably divided as 1 tablespoonful (2 gm) after each meal three times daily Three choline salts are available, i e, choline bicarbonate, choline chloride, choline dihydrogen citrate The bicarbonate and chloride salts can be administered in smaller volumes than the dihy ... molecular

bicarbonate is best tolerated by the g... intestinal tract, and least likely to upset the patient with gastro intestinal symptoms The

choline should be administered for periods of 1 month to 6 months in most cases depending on the clinical progress of the patient

METHIONINE Methionine has been recommended in the past as adjunctive therapy with or instead of choline if desired, in the divided dosage of 6 gm as with choline Methionine comes in tablet form and has been considerably more costly than choline, although used in the same way

Recent studies in patients with cirrhosis by Kinsell et al have demonstrated the unequivocal effect of choline as a lipotropic agent in the treatment of patients with cirrhosis of the liver The studies in these patients were based on the most careful nitrogen balance investigations plus liver function tests ketosteroid estimations, blood chemistries and numerous other clinical and laboratory procedures Choline was conclusively proved to be a valuable adjunct when added to a high protein diet in the therapy of human cirrhosis However it cannot be expected to be of value in reversing the pathologic process involved in a case of terminal Laennec's cirrhosis or biliary cirrhosis as will be described below

These conclusions drawn by Kinsell et al have recently been corroborated by Chaikoff et al in the cirrhosis of the liver induced experimentally in dogs Chaikoff's group has demonstrated that in this disease under experimental conditions the feeding of a

in addition to a high protein diet, the liver cirrhosis promptly disappeared and gave way to a normal liver

Kinsell and his co workers have recently introduced information which demonstrates that in patients with chronic severe cirrhosis of the liver, methionine alone acts definitely as a toxic agent when administered in either oral or intravenous form These investigators have based their conclusions on the results of nitrogen balance studies, and blood methionine levels Morrison came to similar conclusions based on clinical observation and as a result in two previous communications on therapy of cirrhosis, abandoned completely the use of methionine alone in chronic cirrhosis of the liver

LIVER EXTRACT A whole or crude liver extract is administered intramuscularly in a dose of 3 to 5 cc (together with novocain if needed for local pain) daily for 10 days, then every other day for 10 days, and subsequently two to three times weekly as indicated by clinical progress The liver extract is reinforced by vitamin B complex so that each cubic centimeter of liver extract contains at least 10 mg of vitamin B, 0 3 mg of riboflavin, and 10 mg of nicotinamide In addition, one capsule of a high potency multiple vitamin preparation is given three times daily If parenteral liver extract cannot be administered, a useful substitute is prepared by the oral ingestion of 3 to 6 oz of a whole aqueous liver solution or filtrate in fruit or tomato juice before or during each meal This should be taken with 2 teaspoonfuls of brewers' yeast powder three times daily, either with the liver solution or separately as desired by the patient In those patients with an abnormal blood prothrombin time vitamin K is administered orally, 5 mg with 5 grains of bile salts three times daily, parenteral vitamin K may also be administered in 10 mg dosage until the blood prothrombin time has begun or approached normal If this fails to occur after from three to five injections, blood transfusions may be resorted to in order to improve the blood prothrombin time

The oral administration of amino acids has been a useful therapeutic adjunct, provided large and adequate dosage is used No alcoholic beverages are to be taken by the patient

Prognosis On the basis of liver punch biopsies in a series of patients with cirrhosis treated by the author, the following prognostic guide is offered as to the successful outcome or failure of treatment in a given patient

REVERSIBLE CIRRHOSIS OF THE LIVER Favorable prognosis following treatment is possible Cirrhosis of the liver associated with nutritional deficiency in

(1) Chronic alcoholism, early or moderately advanced stages
(2) Chronic ulcerative colitis
(3) Deficiency diseases
(4) Diabetes mellitus

IRREVERSIBLE CIRRHOSIS OF THE LIVER. Poor prognosis following treatment

(1) Biliary cirrhosis
(2) Cardiac cirrhosis, i e, fibrosis of the liver following chronic cardiac congestive failure
(3) Certain hepatic diseases such as Banti's disease, hemochromatosis, parasitic diseases (*Clonorchis sinensis*), etc
(4) Cholangiolitic cirrhosis following chronic infectious hepatitis
(5) *Terminal stage of Laennec's cirrhosis* (small, shrunken, fibrous liver)
(6) Laennec's cirrhosis with superimposed acute necrotic and toxic hepatocellular destruction occurring as a terminal event (Certain cirrhoses such as syphilitic cirrhosis which is now so rare are not described here)

A consistent histologic finding in liver punch biopsies which has characterized the patients responding favorably to treatment of cirrhosis has been the presence of fatty or 'reversible" infiltration and/or fatty degeneration of the hepatic cells Those patients failing to respond to treatment have been usually those without fatty infiltration or fatty degeneration These latter findings are characteristic of those cases formerly known as "alcoholic cirrhoses" It is now well known that in order to produce cirrhosis of the liver alcoholism must occur in the presence of a diet deficient in protein and in vitamin content

Treatment of Ascites This is done by intravenous liver extract, diuretics, paracentesis, or by surgical procedures Recently intravenous liver extract has been employed with some success in the treatment of ascites where other therapy has not been successful The intravenous liver extract (intraheptol-Lederle) is given as a course in the following manner First, allergic sensitivity to the liver extract is tested by the intramuscular injection of from 0 1 cc to 0 2 cc of the concentrated extract, as recommended by Ralli and Labby et al Allergic reactions are rare If no allergic reaction occurs within 30 minutes, a first intravenous dose of 1 cc diluted with 25 cc of saline or 5 per cent glucose solution is given slowly The series of conservative, graduated doses are given as follows

1st day– 1 cc diluted to 25 cc
2nd day– 3 cc " " 30 cc
3rd day– 5 cc " " 40 cc
4th day– 5 cc " " 40 cc
5th day–10 cc " " 50 cc
6th to 14th days–10 cc diluted to 50 cc
Subsequently 10 cc diluted to 50 cc thr times a week

When there is improvement, it may n occur until after the lapse of several weel hence subsequent intravenous liver extra administration depends on the patient progress, some patients have been mai tained for 6 months on injections of the e tract twice weekly The first indication clinical improvement has been improveme in appetite, followed by increase in well b ing and strength The diuretics are given i the manner usually prescribed for heart di ease Paracentesis and the varied surgic procedures for medically intractable ascite are described in surgical texts for the reli of portal decompensation

Bleeding Esophageal Varix The treat ment of hematemesis from bleeding eso phageal varices calls for abstention fro solid or semisolid food until the bleeding ha stopped Bland liquids at room or body tem perature may be taken if the patient's condi tion warrants this, for example, milk, water tea When the hemorrhage has subsided the treatment is similar to that employed in a bleeding peptic ulcer Following the cessa tion of hemorrhage and the establishment of the source of bleeding through esophagoscopic and roentgen examination the esophageal varices may be injected directly according to the technic of Crafoord and Frenckner and Moersch One cubic centimeter of a 2 5 per cent solution is injected at 4 day intervals, requiring four or more injections in a course of treatment Gradual obliteration of the varices may be produced in this way and may require repeated injections if recurrences are encountered Successful results have been described in a number of cases following 5 year progress studies This treatment is understood to be entirely symptomatic and is an adjunct to the treatment of the underlying disease

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HEPATIC INSUFFICIENCY
(Liver Failure)

Acute Hepatic Insufficiency The *acute* form of this disorder may be the result of toxic damage to the cellular structure of the liver The treatment of this condition is discussed under the general heading of acute liver failure The management of acute infectious as well as homologous serum hepatitis, with or without associated jaundice, consists mainly of bed rest and supportive measures Experiments using lipotropic agents (choline and methionine) as well as intravenous injection of liver extract, have not significantly influenced the course of the disease As shown by Havens, there are strong indications that medication with gamma globulin during the preicteric phase of serum hepatitis will prevent the disease in a high percentage of cases Ten cubic centimeters of gamma globulin are administered on two occasions, one month apart, starting one month after blood products were received, for children the dose has to be calculated on the basis of body weight, 0 08 cc per kilogram (Duncan)

Throughout the course of the disease, the daily diet should contain at least 150 gm of protein, 400 gm of carbohydrates, 125 gm

to increase the caloric intake and thus to avoid rapid loss of weight (Hoagland) No evidence has been submitted to substantiate the fact that increase of the protein content of the diet, or restriction of fat intake contributes to the success of therapy (Darmady) Anorexia, nausea, and vomiting, as they may be encountered during the early stages of the disease, require parenteral administration of 5 to 10 per cent glucose in isotonic sodium chloride (1000 to 2000 cc), the amount depending on urinary output, blood chloride and CO_2 levels Urinary output should be kept in excess of 800 cc during each 24 hour period Whenever a lowering of the plasma prothrombin level is observed, parenteral vitamin K (hykinone, 2 4 mg — Abbott), daily for 7 days, is prescribed Opiates and barbiturates are not well tolerated, and should therefore be used only sparingly

It is not advisable for the patient to resume his usual activities until the liver has ceased to be tender, has receded to normal *size, or is at least no more than slightly en*larged and hepatic function has returned to normal, or is approaching normal The latter is best determined by means of the bromsulphalein test, using a 5 mg per kilogram body weight dose, the retention not exceeding 10 per cent after 45 minutes, the icteric index should show a value below 20 units In cases of acute suppurative hepatitis following obstructive jaundice, similar supportive therapy is advised preoperatively (Rosenthal) In amebic hepatitis the foregoing measures have to be augmented by

specific medication in addition to the regimen outlined above *Best results are obtained through* administration of emetine hydrochloride, 0 065 gm intramuscularly daily for 12 days, in conjunction with carbarsone (Lilly), 0 2 mg twice daily for 10 days This course may have to be repeated after an interval of 2 to 4 weeks

Chronic Liver Insufficiency. Sufficient experimental and clinical evidence has been accumulated to prove that the life expectancy of patients with cirrhosis of the liver can be markedly *increased through an appropriate* dietary regimen (Patek and Post, Morrison) A diet of approximately 3600 calories has been advocated, distributed in the following manner 139 gm of protein including the protein contained in brewers' yeast, 175 gm of fats, and 365 gm of carbohydrates The main components of this diet are meat, milk, eggs, fruit, and green vegetables Two generous servings of meat are prescribed, as well as 5 glasses of milk daily, three times with meals and twice in combination with 25 gm of brewers' yeast As some patients will not tolerate yeast, capsules of vitamin B complex are substituted When*ever the blood albumin level is low*, parenteral as well as oral administration of amino acids is indicated Intravenous medication using gelatin and albumin is advocated, even though this measure apparently fails to produce any significant alteration of the serum albumin level

In the presence of ascites, fluids should be limited to 2000 cc, and the salt intake restricted to the extent of eliminating the salt shaker from the tray It is, however, well to remember that with each abdominal tap which may become necessary in order to relieve circulatory embarrassment, an abundant amount of chlorides is incidentally removed *A too rigid restriction* of salt is therefore, liable to precipitate hypochlor-

come necessary, although recent studies have demonstrated that even this measure may not prove successful in all cases Routinely

strated that these lipotropic agents contribute toward the establishment of a positive nitrogen balance Crude liver extract administered either intravenously (intraheptol —Lederle—given daily in gradually increasing doses from 1 to 10 cc, diluted to 50 cc. of 5 per cent glucose), or intramuscularly has led to satisfactory results, although the *manner of its action still remains obscure* Patek and Post suggest intramuscular injection of crude liver extract twice weekly Other methods of treating ascites include medication with mercurial diuretics, especially a course combining mercuhydrin, 2 cc., or salyrgan, 1 to 2 cc, both intravenously once weekly or, if necessary, more frequently with daily administration of ammonium chloride, 3 to 4 gm Abdominal paracentesis may, of course, also become necessary (Barker)

Subcutaneous injection of ergotamine tartrate has been found to relieve pruritus in a certain number of cases (Lichtman) If this *measure should fail to bring relief*, procaine administered intravenously (20 cc of a 0 1 solution in 1000 cc of an isotonic solution of sodium chloride) holds reasonable hope of success For the control of bleeding as well as of ascites, surgical procedures, such as the injection of sclerosing agents into the esophageal varices under esophagoscopy, and ligation of the left gastric vein, have been suggested (Moersch, Patterson and Rouse) Operative anastomosis between the splenic and the renal vein, to shunt a considerable volume of blood away from the portal system, will in some patients relieve portal hypertension, and decrease ascites (Blakemore) Of late, endocrine substances, especially testosterone propionate, have been advocated for their ability to cause nitrogen retention in some instances, but to the pres*ent time only insufficient* evidence as to their beneficial effect has been accumulated

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PREOPERATIVE PREPARATION OF THE JAUNDICED PATIENT

The patient suffering from jaundice of hepatic origin when being prepared for surgery presents a number of important therapeutic problems which must be solved to the best of our ability to minimize the risks of operation Impaired hepatic function must be evaluated restored as far as is practicable and the liver protected against further injury Anemia if present should be adequately treated and thought should be given

possible

The liver parenchyma of the jaundiced patient suffers injury from biliary obstruction infection and various nutritional disturbances and will be subjected to the toxic effects of anesthetic agents and the traumatic insults of surgery in the operative period

Protective measures available include among others the restoration of glycogen stores in the liver There is evidence that a liver generously supplied with carbohydrate food and able to store glycogen is less easily damaged by toxic agents than the glycogen depleted liver The carbohydrate may be

administration of glucose solutions becomes essential Hypertonic solutions of glucose may be used particularly in edematous patients since they promote diuresis and give a considerable caloric intake in small volume Fifty cubic centimeters of 50 per cent solution 200 cc of 25 per cent solution or 1000 cc of 10 per cent solution may be given at one time intravenously and repeated at intervals Where edema is not a problem 1000 cc of 5 per cent glucose may be given either intravenously or subcutaneously

ago by Peyton Rous For this reason an adequate protein intake or the administration of choline or inositol should accompany any prc'

is

diabetes mellitus will usually require the use of insulin in the preoperative preparation of any jaundiced diabetic patient Regular insulin may be added to parenteral glucose solutions in the amount of 1 unit to each 2 or 3 gm of glucose This is usually advisable in the diabetic patient receiving glucose infusions and may also be of some value in nondiabetic patients in the preoperative period

Another protective measure for the jaundiced patient being prepared for operation is the provision of an adequate intake of protein The rate of depletion of liver glycogen in the fasting animal is less rapid if a generous protein intake was given previously The amino acid methionine present to the extent of about 3 per cent in most of our common food proteins protects against the development of fatty liver Many of our protein foods also contain some choline another protection against the fatty liver Protein is necessary for building hemoglobin for the manufacture of blood cells and for

the production of the plasma proteins and the replenishment of the protein stores of all the body tissues Depleted plasma albumin often an accompaniment of severe liver damage may render the jaundiced patient more susceptible to pulmonary edema and to shock in the postoperative period

tolerated it is often feasible to insure an ample intake of protein in liquid form Suggestions for both solid and liquid diets for jaundiced patients will be given later in this article

If adequate oral feeding is not possible we must resort to parenteral administration of blood and its products or amino acids Transfusions of 500 to 1000 cc of whole blood or of 1 to 2 units of plasma or plasma albumin may be given daily or more frequently when speed is essential in preparing the patient for operation Various preparations of amino acids such as amigen may be given as 50 gm dissolved in 1000 cc of 5 per cent glucose or normal saline and administered slowly intravenously Rapid administration may give unpleasant reactions Our aim should be to raise plasma albumin above 3 5 gm per cent in the patient s blood stream and total proteins above 6 0 gm per cent

Periods of protein starvation caused by anorexia and vomiting alcoholism and various types of chemical injury including chloroform anesthesia lead to the production of fatty infiltration of the liver The value of a high protein diet in treating this condition has already been mentioned Some restriction of fat intake to 1 gm per kilogram of body weight per day or less is probably advisable The caloric needs are met by increase in the dietary carbohydrate Other valuable aids in the prevention and treatment of fatty liver are the lipotropic agents *choline* and *inositol* Both show little evidence of toxicity in the dosages here recommended

Choline chloride and choline bicarbonate being deliquescent are best given as liquid preparations with various flavoring syrups (e g , syrup of orange with the chloride) in doses of from 1 to 6 gm daily Choline dihydrogen citrate is available in tablet form (0 6 gm each) One or 2 tablets may be or dihydrogen citrate will usually overcome any tendency to gastric distress

Inositol in my experience causes no gastric distress It has been administered either in capsules containing 0 3 to 0 5 gm or in powdered form mixed with food The dosage given has been 1 to 3 gm daily

Anemia is frequently found in hepatic disease It may be due to faulty storage of the antianemic factor of liver in the damaged organ Protein starvation recent hemorrhage or an associated splenic abnormality may also contribute to its causation Treatment depends on the underlying cause Liver extract should be administered orally (e g as lextron 2 capsules three times daily) or parenterally in a dosage of 1 to 5 units hypodermically daily if the anemia is of the macrocytic type Ferrous sulfate in a dose of 0 2 gm three times daily is indicated in hypochromic types of anemia If the period of preoperative preparation must be brief it will be necessary to resort to blood transfusion The erythrocyte count should be raised by these methods above 4 000 000 and the hemoglobin above 12 gm per 100 cc prior to operation if possible

Protection against shock is afforded by restoration to normal of the plasma proteins and the cure of anemia by establishing fluid balance and attention to nutritional needs for minerals

Protection against hemorrhage in the postoperative period requires the correction of any defects in the clotting mechanism and the capillary walls noted during the preoperative study of bleeding time clotting time prothrombin time platelet count and capillary fragility Of these the jaundiced patient is most likely to have a low level of blood prothrombin The reason for this is that the exclusion of the bile salts from the intestinal tract which commonly occurs in obstructive jaundice brings about faulty absorption of vitamin K In severe liver injury this organ may be unable to utilize vitamin K in the production of prothrombin even though the vitamin is available in adequate amounts Discovery of a low prothrombin

blood level indicated by a prolonged prothrombin time calls for the administration of some form of vitamin K Synkamin may be given orally in a dosage of 4 0 mg three times daily Either synkamin or menadione may be given in similar dosages by hypodermic or intramuscular injection If the low prothrombin *is due to faulty absorption* these preparations usually produce prompt improvement If impaired hepatic function is the cause they may be ineffective Prothrombin in such cases may be temporarily supplied by blood transfusion

Cases with evidence of increased capillary fragility should be given rutin orally in a dosage of 20 to 40 mg three times daily Vitamin C should also be given in a dose of 100 mg twice daily either by mouth or by parenteral injection

Thrombocytopenia is treated by rutin and by transfusion of blood but if severe and persistent may call for consideration of splenectomy

The *diet* of the jaundiced patient in the preoperative period should be planned with the following considerations The caloric intake should be high in the patient of subnormal weight averaging at least 35 calories per kilogram of body weight using the patient s normal body weight as the basis of calculation In the patient of normal weight caloric intake may be held at 25 to 30 calories per kilogram and in the obese patient should be reduced to 18 to 20 calories per kilogram again using the ideal weight of the patient as the basis of calculation

Protein intake should be relatively high averaging 1 25 to 1 5 gm per kilogram of ideal weight In those who are underweight or normal in weight fat is held to a level of about 1 0 gm per kilogram of normal weight *The remainder of the caloric allowance* is made up by carbohydrate and will usually average 4 to 5 gm per kilogram of

allowance is made up by carbohydrate Reducing d ets are of value only if the surgical condition permits a preoperative period of sufficient length to allow weight reduction to occur Cases that have been subjected to a reducing diet should have a more generous carbohydrate intake in the last few days prior to operation

If the patient is unable to eat solid food it is entirely feasible to prepare a palatable high protein liquid diet which will meet the above requirements The following formula has been prepared and used successfully by the Department of Dietetics of the St Mary s Group of Hospitals of St Louis University

Liquid Diet Whole milk 1000 cc dry skim milk 120 gm eggs 2 100 gm egg yolks 3 60 gm sucrose 80 gm lactose 40 gm dextromaltose No 2 20 gm vanilla extract 15 0 cc water to make 1200 cc Add to this thiamine 1 0 mg niacinamide 12 0 mg ascorbic acid 100 mg and ferrous sulfate 12 0 mg

This supplies about 2050 calories protein 100 gm fat 70 gm and carbohydrate 250 gm To reduce fat further the egg yolks may be omitted and the caloric loss made up by additional lactose and dextromaltose

Occurrence of cheilosis glossitis neuritis pellagrous skin lesions and spider web venules calls for the administration of larger doses of the vitamins of the B complex than are described above given as tablets of fortified yeast 3 to 6 daily or parenteral injections of solutions of the mixed vitamins A fortified fish liver oil containing vitamin A 10 000 units and vitamin D 1000 units is an additional desirable dietary supplement

Parenteral infusions of isotonic solutions of sodium chloride or sodium lactate are of value in supplying fluids to dehydrated patients They are essential in restoring the body s stores of sodium where these have been depleted by diarrhea excessive sweating or adrenal insufficiency Calcium gluconate 1 gm three times daily in tablet *form or by intramuscular or intravenous injection* should be given if the blood calcium is low

Antibiotics of appropriate type should be employed to control any actual infection found Administration of penicillin 300 000 units in a slowly absorbable form may be begun as a prophylactic injection before operation and continued into the postoperative period When the cost reaches lower levels aureomycin also may be used as a prophylact c against infection

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Direct observation on experiment carried out at the Rockefeller Institute in 1921

ACUTE CHOLECYSTITIS

The occurrence of an acute infection of the gallbladder presents the surgeon and the internist with a problem of considerable difficulty and one which requires careful judgment in its solution Mild catarrhal cholecystitis may quickly subside spontaneously or the inflamed organ may be removed surgically without too great difficulty The more *severe forms of infection* purulent and gangrenous cholecystitis have much more serious aspects The surgeon often hesitates to operate while the inflammation is acute because the involved tissues of the gall bladder wall are in many instances so friable as to render removal difficult Simple drainage which ordinarily can be carried out even in these circumstances without undue risk leaves behind a pathologic gallbladder which is likely to be the future site of the formation of calculi Hence a delay in surgical inter [illegible]

infection into the peritoneal cavity If the cystic duct is patent while the common duct is obstructed bile also may escape into the abdominal cavity a condition which greatly increases the gravity of the prognosis

The patient suffering usually from severe pain in the right upper abdominal quadrant with associated anorexia nausea and vomiting must be nursed carefully through the period of the acute infection weighing carefully the symptoms and physical signs from day to day to decide the proper time for *operation* Meanwhile the liver must be protected as well as possible from functional impairment so as to render the surgical procedure as safe as possible when it becomes necessary or desirable The nursing staff as well as the *attending physician* should be alert to recognize any unfavorable changes in the patient s condition

The general care of the case of acute cholecystitis involves many of the principles discussed in the Preoperative Preparation of the Jaundiced Patient In the early acute stages the patient as a rule will tolerate but little food Parenteral administration of fluids to prevent dehydration often is necessary in this period Glucose, 5 per cent solution in distilled water or isotonic sodium chloride solution may be used However the necessity of maintaining nitrogen balance and preventing protein starvation is even more *urgent in the presence of an acute infection* than in the case of uninfected biliary obstruction For this reason blood plasma or amino acid *solutions should soon* be added in any case unable to tolerate oral ingestion of proteins The high protein liquid diet described in the preceding section should be given as soon as it can be tolerated later gradually introducing more solid food Fat causes gallbladder contraction and should be avoided

If the patient is anemic transfusions of whole blood should be administered and liver extract 5 units daily given by hypodermic injection As soon as nausea is not present iron in the form of ferrous sulfate 0 2 gm three times daily should be prescribed

The prothrombin content of the blood should be determined and if a deficiency is found vitamin K in the form of synkamin or menadione is to be given orally or parenterally in a dosage of 4 mg three times daily

Fatty liver is to be avoided by use of a high protein high *carbohydrate and* low fat diet and by the administration of choline and inositol Choline may be given as the dihydrogen citrate one 0 6 gm tablet three times daily after meals with amphojel 15 cc Inositol in a dosage of 3 gm daily may be given as a powder mixed with food

Besides the maintenance of nutritional status the treatment of acute cholecystitis also includes measures to combat the existing infection If this can be accomplished promptly it lessens the danger of rupture of the inflamed gallbladder and will hasten the return of the tissues to a more healthy state

The patient should be kept at rest in bed but with frequent change of position from

r demerol (0 1 gm) by hypodermic in ection

The introduction of the antibiotics has sup lied the physician with measures which educe the risks of this type of infection There still remains however, the problem of ecuring sufficient penetration of a sac like structure such as the gallbladder by the antibacterial agent Also the type of organ ism causing a given infection of the gall bladder is usually difficult to determine This renders the choice of the most effective antibiotic uncertain The most common in

penicillin However the gram positive pyo genic cocci, streptococci, pneumococci, and staphylococci may occasionally infect the gallbladder In these cases penicillin may be quite effective

If it is decided to use sulfa drugs a combination of equal parts of the three sulfa

one alone The fluid intake should be main tained at a level of at least 3000 cc per day Sufficient alkali to insure alkalinization of the urine is desirable to reduce further the risk of crystal formation in the kidneys Blood counts should be done daily to note any suggestion of toxic effect on the blood forming organs such as agranulocytosis or hemolytic anemia An initial dose of 4 gm should be followed by 1 gm every 4 hours

Penicillin may be administered in aqueous solution in a dosage of 40 000 to 50 000 units every 4 hours or as procaine penicillin in aqueous or oily menstruum as an intramuscular injection of 300,000 units once or twice daily

Streptomycin is more likely to be of value in infections due to gram negative bacilli This antibiotic must be given with some caution because of possible allergic reactions and toxic effect on the eighth nerve and labyrinth in the form of impaired hear-

fewer allergic reactions The dosage of both streptomycin preparations is usually from 1 to 2 gm daily The daily dose is divided into three or four equal parts and given at 8 or 6 hour intervals If any vestibular symptoms or impairment of hearing appear the drug should be discontinued

Aureomycin offers some promise as an agent which should be effective against many of the types of infection which involve the gallbladder It is administered orally in dosages of from 50 to 500 mg per kilogram of body weight per day It is given at 4 hour intervals for the first 24 hours and then every 6

its use

These agents must be watched closely for their effect on the patient's symptoms and physical findings as well as the changes in fever leukocyte count and sedimentation rate By this means a decision is reached regarding the progress or suppression of the infection If the infection is successfully overcome, operation is usually postponed for a period of several weeks All of the pre cautions described in the preoperative care of the jaundiced patient should be exercised during this waiting period Should it be decided that operation will not be done, even after the infection has subsided, the treatment then becomes that which will be described under the section on Chronic Non calculous Cholecystitis

Goronwy O Broun

CHRONIC NONCALCULOUS CHOLECYSTITIS

The problem of chronic noncalculous cholecystitis differs from that of acute cholecystitis because the infectious process is usually mild and presents little danger of rupture and peritonitis The chief complica tion likely to arise is the formation of calculi To this must be added the possibility that chronic irritation may favor the occurrence of neoplastic changes with resultant cancer of the gallbladder or bile ducts The chronic

recurrent inflammatory react
cause ann
and more

The symptomatology includes repeated attacks of pain in the right upper abdominal quadrant with aggravation of symptoms after ingestion of fatty foods During cholecystography failure of visualization, poor concentrating power, and failure to empty after a fat meal are suggestive evidences of the existence of chronic cholecystitis Calculi cannot be dissolved by medicinal treatment In the

trial of medical care can legitimately be attempted

The principles underlying the medical measures usually suggested are promotion of increased flow of bile, relaxation of the sphincter of Oddi, and stimulation of gall bladder contraction In the alternate filling and emptying of the gallbladder, the hope is that drainage of inflammatory products will be promoted, the bile ducts cleared of debris, and any small precipitates that might be future nuclei of stones flushed out from the organ

It is probably unwise to make use of this form of treatment during any period in which acute symptoms are present The treatment of such a period should follow closely the suggestions given for the treatment of acute cholecystitis, particularly rest in bed, relief of pain by sedation or opiates if necessary, a low fat diet and use of antibiotics if active infection appears to be present When acute symptoms have subsided, it then becomes feasible to attempt to clear the biliary tract and attempt to restore the gallbladder to normal function

Administration of preparations of bile salts is among the most effective methods of increasing the fluid output of bile Preparations such as bilron ketochol, or decholin in a dosage of 0 25 gm three times daily after meals may be given Since the discovery of Meltzer and Auer that magnesium sulfate causes relaxation of the sphincter of Oddi and contraction of the gallbladder, the use of saline cathartics in the treatment of chronic cholecystitis has had some justification Magnesium sulfate (60 cc of 33 per cent solution) may be given orally in a glass of water or may be given directly into the duodenum through a duodenal tube Sodium sulfate or sodium phosphate (4 gm) may also be given Perhaps the most palatable preparation is the effervescent solution of magnesium citrate (200 to 350 cc) The saline laxatives are best given in the morning before breakfast

Spasm of the sphincter of Oddi may be a complicating factor in cholecystitis Nitroglycerin (0 0006 gm), sodium nitrite (0 06 gm) and theophylline ethylene diamine (0 1 gm) are substances believed to have the ability to relieve spasm They may be given three times daily after meals with bile salts

Fat is one of the most powerful agents

infection is acute but in the stage where

of these substances may be given three times daily before meals One reason for caution in the use of fats even in quiescent stages of cholecystitis is the belief that high fat diet favors the formation of biliary calculi However, if coupled with bile salt administration there is probably not too much danger of calculus formation

Goronwy O Broun

DISEASES OF THE PANCREAS

ACUTE PANCREATITIS

Acute pancreatitis implies an acute inflammation resulting from the action of pancreatic enzymes within the injured ducts of the pancreas The varying types of acute pancreatitis were classified by Pratt as follows (1) acute pancreatic edema (2) acute pancreatic necrosis with or without hemorrhage, and (3) suppurative pancreatitis (abscess of pancreas) Many other students have accepted his classification

After the acute episode has passed, the patient should be carefully observed to de-

ermine the etiology Rich and Duff believe hat the majority of cases of hemorrhagic pancreatitis result from partial obstruction of the small ducts owing to metaplasia of he ductal epithelium resulting in rupture of the small ducts The freed pancreatic ferments by their digestive action destroy local arteries and veins and hemorrhage occurs If no blood vessels are affected the local tissue becomes edematous This theory

edema of the pancreas acute hemorrhagic pancreatitis and acute pancreatic necrosis The role played by the biliary tract in the average case is questionable and in view of the above concept is rarely a prime etiologic factor This concept permits a much different approach to the management of acute pancreatitis from that in vogue in the early decades of this century

Experience however cannot fail to impress one with the high coincidence of gall bladder disease with acute pancreatitis and the fact that there is a relationship between the two has long been recognized Sixty per cent of cases of acute pancreatitis are accompanied by biliary tract disease and it may be further assumed that a certain percentage will be associated with common duct obstruction from stone in the ampulla of Vater or reflex from spasm of the sphincter of Oddi The action of enzymes on the tissues in the presence of an obstruction of the pancreatic biliary tract system may account for the acute disturbance

Acute pancreatic hemorrhage and necrosis have also been shown to be caused by obstruction of the pancreatic ducts occlusion

Too frequently acute pancreatitis is confused with primary acute biliary tract disease It must also be differentiated from coronary occlusion perforating peptic ulcer intestinal obstruction and renal calculus Routine performance of serum amylase tests in all cases of acute abdominal disorders greatly increases the accuracy of diagnosis This of course is of the greatest importance since it is now almost universally agreed that acute pancreatitis should be treated conservatively

Active Treatment As previously indicated the pathologic process varies with the particular circumstance in the pancreas Acute edema or even mild hemorrhage may subside within a few days without any major complication A large hemorrhagic process may be followed by local necrosis Any of these may resolve satisfactorily without the necessity of any surgical interference On the other hand when the process is extensive and followed by shock and vasomotor collapse the problem is one of an acute emergency and demands every aid Some of these patients may die within a few hours of onset These individuals should not be operated on since in this state of collapse surgery will most certainly be fatal A much lower mortality is maintained in such severe cases with the ultraconservative program Perhaps the most difficult decision to make is the decision not to operate when the patient is so ill with an intra abdominal catastrophe

As soon as the diagnosis of acute pancreatitis is made certain supportive measures must be instituted The general management is directed toward the presenting symptoms In mild attacks hot fomentations should be applied to the epigastric area and continued constantly An enema of warm physiologic saline often brings relief of the distention and discomfort

When the attack is severe pain and moderate shock must be dealt with Morphine sulfate ¼ grain (15 mg) is given and repeated in one hour if necessary for pain

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pain and less likely than morphine to cause sphincter contraction If morphine is given atropine sulfate 1/100 grain (0 6 mg) should be combined with the first dose to control pylorospasm and other sphincter contraction Relief from pain may also be obtained by slowly injecting intravenously 10 cc of a sterile 10 per cent solution of calcium gluconate This may be further justified since it is reported that there is a decrease in blood calcium values in acute pancreatic necrosis Papaverine and atropine are both effective in diminishing secretions of the

pancreas and relaxing the sphincter of Oddi

Nausea, vomiting, and dehydration, which so often accompany the severe attack, result in disturbances to the general body chemistry In order to evaluate properly the electrolyte and serum protein balance the following studies should be immediately undertaken blood count and blood typing, blood chemistry studies to include serum proteins, pancreatic ferments, chlorides, calcium, and CO_2 combining power

The severe attack should be combated by intravenous administration of 1000 cc of 10 per cent glucose in normal saline solution When the blood volume and cells have fallen or the serum proteins are at a critical level, 500 cc of whole blood or plasma should be given as a transfusion and repeated every 24 to 48 hours until the critical stage has passed and the blood levels return to a reasonably normal status

Gastric dilatation and ileus are best controlled by Wangensteen continuous suction or by introduction of the Miller-Abbott tube

Inasmuch as infection plays a part in some cases, penicillin 50 000 units intramuscularly every 3 hours, and sulfonamides intravenously or by mouth may be given until the bacterial invasion is under control

Ascorbic acid, 500 mg, and injectable *vitamin B complex, both given intravenously* once daily, may aid in more rapid convalescence In the presence of jaundice, vita-

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ferments in the pancreas Magnesium sulfate, 30 cc to 60 cc of 30 per cent solution by nasal tube four times daily for several days, facilitates biliary flow into the duodenum

Since all foods must be withheld for several days it may be necessary to supply

At first such foods as thoroughly cooked strained cereal *rice, and fruit juice* may be tried in small amounts at frequent intervals If these foods are well tolerated, it is desirable to return to a general diet consisting of high carbohydrate, *low protein*, and low fat The usual hydrolysates are recomme because of ease of digestion

If constipation is present, 1 or 2 dra sodium phosphate in a glass of hot *before breakfast is indicated to aid b* function and drainage of bile and pa atic secretions into the duodenum

A small single dose of roentgen ray pears to inhibit amylase enzyme produ and minimize the degree of pancreati sue destruction

A practice worth following is to op only when there is reasonable doubt the diagnosis or when it becomes ev

to investigate further the cause of pa atitis One may be reasonably safe wit *diagnosis if a careful study is made o* onset and progress of the case, and t result of the serum amylase test is awa If there is reasonable doubt in the diag the patient should not be refused the be of abdominal exploration, and if the nosis of acute pancreatitis is found co the minimum of surgery should be u taken and the pancreas left alone Wher dence of local necrosis or abscess is pre and surgery is deemed imperative, *measure must be instituted to raise th* tient's health status to permit sur Proper drainage of the necrotic process then be undertaken

In the presence of gallstones or pers jaundice, operation should be perfo when the patient seems to have reach maximum of recovery Duodenal dra by Lyon's method has been instituted undetermined but suspected biliary disease has been considered Because o relatively high incidence of biliary tract ease in acute pancreatitis, there is reason to remove all gallstones as a phylactic measure

LOWELL D SNO

CHRONIC PANCREATITIS

Chronic pancreatitis results from a vious episode or repeated episodes o inflammatory process, from degener changes in the pancreas from syp chronic nephritis, or arteriosclerosis, or *inflammation from contiguous organs*

a disorder observed clinically with relative infrequency

The symptoms are often confused with those of disorders of the intestine or of gall bladder infection Chronic pancreatitis usually reveals itself by attacks of distress discomfort, or pain in varying intensity in the epigastric region, and the presence of large, bulky, fatty malodorous gray stools The stools when examined reveal fatty acid crystals and soaps and at times undigested muscle fibers

In the advanced state marked disturb ances in nutrition are observed Jaundice is sometimes seen and glycosuria is occasionally present Roentgen studies may disclose pancreatic calculi

Active Treatment The general manage ment of chronic pancreatitis is dependent on the many factors which must be considered causative Since the symptoms are often as sociated with biliary tract disease or disease of adjacent structures which has contributed to the inflammation of the pancreas, these conditions must also be considered in treatment Conservatism is the policy, although no hard and fast rule can be made or adhered to

Pancreatic insufficiency occurring after marked destruction of the pancreas, either in acute pancreatitis or in the more slowly de

restriction is the rule

Diet is in most cases the important aspect of treatment Diet may or may not be se verely restricted, depending on the evidence in the stools of inadequate digestion of fats, protein, and carbohydrates As a rule, more than one ferment is deficient but digestion of fats is particularly disturbed At first a fat free diet should be planned avoiding roughage and high cellulose foods, Steatorrhea is usually promptly controlled, although it is not necessary that fat disappear completely from the stools since a little fat is usually without irritating effect The undigested fatty acids increase acidity in the intestine, which results in secondary diarrhea Usually skimmed milk, gelatin, finely ground lean meats soft boiled egg, hydrolyzed milk proteins, vegetable purées, tapioca, cottage cheese, rice, well cooked farina, cream of wheat, corn meal mush, strained oatmeal, and melba toast are included in the diet Citrus fruit juices and strained cooked fruits may be taken in small amounts All fluids should be given warm Hydrolyzed proteins and protein milk, although low in calories, promptly satisfy the protein starvation

The total caloric content is insufficient on the above foods unless the patient is fed every 2 to 3 hours

Achlorhydria is a common finding and when present requires dilute hydrochloric acid It may be given in 10 to 20 minims three times daily before meals, in ½ glass (100 cc) water

Pancreatic extract U S P , 10 grains, (150 mg), preferably in enteric coated tablets, before or with meals three times daily, is essential Raw ground pancreas, although difficult to take has been fed to patients with good results

Tincture of belladonna 10 drops, or extract of belladonna, ¼ grain (15 mg), three times daily after meals may be given for intestinal unrest

Calcium carbonate 15 grains (1 gm), three times a day half an hour before meals is useful because it binds the free fatty acids, powdered extract of opium ½ or 1 grain (30 to 60 mg), three to four times daily, or tincture of opium U S P , 5 to 10 drops four times daily, may be given to control the diar rhea

Since one of the major complications in chronic pancreatitis is disturbance in nutri tion the following are recommended liver extract (15 units 1 cc intramuscularly, once or twice weekly) folic acid brewers' yeast tablets or yeast extract, vitamin B complex, injectable 1 cc intramuscularly or synthetic preparation for intravenous administration, ascorbic acid 500 mg intravenously once daily Many of these may be given less often as the nutritional status improves, but should be continued indefinitely as indicated

The stools should be studied and carefully followed to observe the effect of treatment

Moderate to strict dietary supervision is followed by gratifying results Nutrition is improved and the stools may return to a fairly normal state, although remissions are frequently observed after dietary indiscre-

tions or following mild exacerbations of sub acute attacks of pancreatitis One patient, observed over a period of twenty years, is maintained today on a moderately restricted *diet and an adequate amount of pancreatic* extract Another patient, who recently died at the age of 82, was known to have shown signs of chronic pancreatitis for more than 20 years, and in his latter years developed diabetes and had numerous calculi in the pancreas but remained in a state of good nutri *tion with only moderate dietary restriction*

Experience justifies the conservative, non surgical procedure Rarely is the problem of pain so severe as to require operation, al though no patient should be denied radical surgery when other measures for the control of pain fail The presence of pancreatic cal *culi is not an indication for operation unless* pain and obstructive symptoms make it im perative The relative frequency of the find ing of pancreatic calculi by roentgen studies in patients with few symptoms would seem to preclude the need for their removal as a routine procedure

Biliary tract disease, gallstones, obstructive jaundice, and chronic perforating peptic ulcer, or suspected pancreatic carcinoma should all be dealt with by proper surgical measures

LOWELL D SNORF

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CELIAC SYNDROME

The term "celiac syndrome' includes several clinical varieties of a disorder in which the essential feature is a defect in fat absorp tion Celiac or Gee Herter-Heubner disease in early childhood has its counterpart as sprue in adult life Each disorder has as its major sign idiopathic steatorrhea or fatty diarrhea The stools contain large amounts of fat in the form of fatty acids and soaps, and these cause intestinal irritation and diar rhea Carbohydrates are sometimes poorly handled, although this failure is not the re sult of a defect in absorption but of a dis turbance in intestinal function

Sprue must be considered as a deficiency disorder superimposed upon an already defective organism disturbed by infection

between celiac disease and sprue is the age of the patient affected

Active Treatment Since the etiology of celiac disease and sprue is unknown treat ment must be directed to avoidance of precipitating factors, to symptomatic man *agement of defects in fat and carbohydrate digestion, to specific management of acute* crises, and to control of secondary disturbances related to nutritional deficiencies Treatment is similar in both adults and chil dren, the major difference being in amounts of medication and food given Dietary and supplementary considerations are identical In general, *all other factors* of management are subordinate to liver therapy and diet

Acute gastro enteritis may precipitate an acute crisis at any age Questionable foods and contact with contagious and *infectious* diseases should be avoided When infectious disease is present, daily injections of paren teral penicillin, 300 000 units of the depot

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In the infant, child, or adult with celiac crisis, oral fluids are to be withheld and the fluid and electrolyte balance controlled by parenteral administration Intramuscular liver extract, calcium gluconate, vitamin B complex, and vitamin C parenterally are given as early as possible and continued daily until the stomach and intestine are found tolerant to them and food The specific dosage of these substances is discussed later

From this point on and to control the chronic state, management by diet, liver extract, vitamins, and mineral supplements is of utmost importance Emphasis is on a heavy protein diet, low in fat *and restricted* in carbohydrates Foods should be easily as similable and require minimal functional

efforts of the intestine In children the diet at first should consist of protein milk amino acids or protein hydrolysates in broth or bouillon gelatin with fruit flavor weak tea and warm or hot water Later the following may be added finely ground lean beef minced white meat of chicken cottage cheese puréed spinach, squash, celery green beans and asparagus tips

If the stools tend to loosen after the above additions the quantity of vegetables should be reduced As the stools continue to have a normal consistency more vegetables should be given and citrus fruits and cooked canned and puréed fruits such as pears peaches and apricots may be added Banana or banana powder has long been recognized as a well tolerated fruit

There may now be a gradual transition to a fairly normal and adequate diet Butter and whole milk should be added with the greatest caution Milk is usually poorly tolerated a fact which suggests an allergy component and which demands further study The stools should be regularly analyzed especially with the increase in fats to determine if these additional foods are being digested Inasmuch as carbohydrates are at times poorly digested such starches as potato and rice are to be cautiously added and stools checked for starch granules If there is increased fermentation in the stools carbohydrates must be reduced

Since the prescribed diet provides a low caloric intake it is necessary to find the carbohydrates and fats best suited to the individual desires and tolerance and add them as rapidly as possible Protein hydrolysates as protein supplement have been found to be of inestimable value

The intestinal functional balance is often sensitive and may be upset by emotional disturbances and fatigue and too rapid additions to the diet The patient should always be cautioned to eliminate foods to which he has previously found himself sensitive and this should be further emphasized if there is a history of allergy Fats in the form of fried foods gravies and oily fish should be avoided and the quantity of all fats should be limited

Recurrence of characteristic symptoms at any stage demands immediate modification of the diet

Vitamins may be given as concentrated fish liver oil 5000 to 10 000 international units daily provided it is tolerated Ascorbic acid in citrus fruits and tomato juice, or 100 mg tablets two to three times daily should be administered Brewers yeast powder folic acid or a liquid yeast extract or vitamin B complex will supply vitamin B

Liver extract or vitamin B complex injectable is given two to three times weekly at first and usually 1 cc of liver extract is advised to be taken once a week parenterally for an indefinite period Crude liver or the concentrated form is equally effective The new vitamin B_{12}, 30 micrograms three times a week may prove to be more effective than liver extract

Alcohol is harmful and must be avoided as should laxatives Transfusion is rarely necessary

Remission of intestinal symptoms and improvement in the nutritional status often occur with dramatic promptness Proof of the adequacy of the regimen is noted first in the change in the character of the stools They are less frequent contain more color and less

The child or adult with celiac syndrome usually is faced with a long and discouraging trouble The active phase with its outstanding symptom of defective fat absorption is followed by invalidism anemia and mineral vitamin and protein deficiency unless early well chosen and prolonged therapy is instituted Inadequate treatment leads to chronic invalidism and the disease may in fact result in death when not treated early or thoroughly enough

The celiac syndrome must be considered a chronic disease and the patient requires constant strict supervision and control to avoid the recurrences so often precipitated by emotional bouts intercurrent infections and sundry intestinal upsets

LOWELL D SNORF

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CHAPTER VII

DISEASES OF THE RESPIRATORY TRACT

DISEASES OF THE TRACHEA AND BRONCHI

ACUTE AND CHRONIC LARYNGITIS

As a rule laryngitis requires only symptomatic measures for treatment The most specific remedy is voice rest Most of the treatment is directed at the accompanying symptoms of the upper respiratory tract infection A few days of bed rest are usually indicated and this should be in an atmosphere free of chemical and physical irritants such as noxious fumes and dusts Smoking and the use of alcoholic beverages should be forbidden The diet may consist of any food desired, but *liquids and soft foods* are usually more appetizing and better tolerated during the acute stage Iced drinks and cold foods such as ice cream are soothing

Local applications of warm or cold compresses may make the patient more comfortable In the presence of nasal congestion, one of the various popular nose drop preparations may be prescribed for symptomatic relief General malaise and fever usually can be controlled with 10 grains (0 65 gm) of acetylsalicylic acid The use of codeine in ¼ (15 mg) or ½ (30 mg) grain doses every 4 *hours may be necessary to relieve* more severe discomfort or annoying and irritating cough One quarter (15 mg) or ½ grain (30 mg) doses of phenobarbital, 10 (0 65 gm) or 15 grains (1 gm) of a satisfactory bromide or any other suitable sedative may be used to prevent restlessness Larger doses are required to relieve insomnia

[illegible] the most effective and

and husky or the patient is able to speak only in a whisper, there should be a minimum of conversation and preferably none Rest of the vocal cords should be stressed above all else in the treatment of laryngitis Steam inhalations produce soothing symptomatic relief Compound tincture of benzoin, 1 teaspoonful to a pint of water, makes the inhalation more pleasant The steam may be produced from an electric water vaporizer or from a simple steam kettle Inhalations for periods of 20 minutes several times daily are frequently beneficial

Antibiotic or sulfonamide preparations are rarely indicated However, in the presence of debility, an overwhelming infection, or other significant complications, *penicillin* streptomycin, other antibiotics, or a suitable sulfa drug, singly or in combination, may be indicated in full therapeutic doses Penicillin and sulfa drug lozenges have small value in the treatment of even mild laryngitis At times laryngitis may require the direct application of shrinking solutions or other therapeutic agents such as 0 5 per cent silver nitrate Recourse to this procedure is rarely indicated since the simpler measures already discussed are usually effective Antihista [illegible] ally or

frequently useful in inflammatory disease the larynx A suitable antibiotic administered with benadryl is a satisfactory and effective combination (see section on Bronchitis and Bronchiectasis) With subsidence of the acute symptoms, the same precautions and treatment should be followed during the first few days of convalescence If there is a recurrence of symptoms, the management is the same

In chronic laryngitis the principles of treatment are generally similar but must be administered over a longer period of time If laryngitis persists in spite of adequate ther-

apy the vocal cords should be visualized either with a mirror or even better by direct laryngoscopy This is done to rule out the possibility of laryngeal tumor tuberculosis syphilis or other serious disease entities Treatment in these instances is more specific but frequently futile In some cases of chronic laryngitis it becomes necessary to retrain the voice This is especially true of public speakers and singers with a history of recurrent and troublesome laryngitis

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Sandy B Carter

ACUTE TRACHEOBRONCHITIS

bed a few days until the symptoms begin to clear In the presence of fever bed rest is mandatory In any event the infection will be more easily and quickly controlled if the patient remains in bed in a warm and well ventilated room free of chemical or physical irritants Smoking and dust are to be avoided Dietary restriction is unnecessary although during the acute stage a liquid or a soft diet will usually be more palatable Fluids are frequently forced and alkalis recommended However there is no proof that either of these measures is of any therapeutic value Steam inhalations should be prescribed for 20 minute intervals three or four times daily These can be administered from an electric water vaporizer or an ordinary steam kettle One teaspoonful of compound tincture of benzoin may be added to each pint of water to be vaporized This practice produces a pleasing aroma but actually the steam is primarily responsible for any resulting symptomatic improvement

Acute tracheobronchitis is usually accompanied by nasal congestion and drainage This annoying complication demands attention since the nasal discharge will gravitate into the trachea and bronchi and produce additional signs and symptoms Numerous proprietary sympathomimetic preparations are available for relief of the nasal symptoms We prefer privine hydrochloride A host of proprietary nasal drops with an added antibiotic or suitable sulfa drug are also available but the specific therapeutic benefits claimed for these combining types of nose drops are probably exaggerated Three to 5 drops of privine hydrochloride in each nostril three or four times daily are usually sufficient to control the nasal symptoms No sympathomimetic nose drop should be prescribed in the presence of such acknowledged contraindications as hypertension hyperthyroidism or diabetes mellitus In these instances a satisfactory measure of relief can be obtained with warm saline irrigations Chloresium nasal drops produce satisfactory symptomatic relief and do not possess any of the undesirable sympathomimetic qualities At no time should the use of nose drops in an oily base or a nasal jelly be prescribed The danger of a complicating lipoid pneumonia especially in the very young and the aged far exceeds the possible therapeutic benefits which may be expected from this practice Interference with ciliary activity is an added disadvantage The addition of an antihistaminic agent to any of the acceptable sympathomimetic nose drop preparations appears

cient to control general malaise If this is not effective ¼ (15 mg) or ½ grain (30 mg) of codeine can be administered in addition. Relief of restlessness and insomnia may be accomplished with the use of adequate doses of a satisfactory barbiturate or bromide Cough may be the most annoying symptom in tracheobronchitis No treatment is needed for mild cough If the secretions are excessively thick and tenacious expectorants are required to combat useless cough and resulting discomfort Expectorants should be used only when specifically indicated Injudicious use of expectorant drugs may mask *the clinical symptoms or actually* cause spread of infection as a consequence of the increased production of watery bronchial secretions Profuse and tenacious bronchial secretions may cause respiratory embarrassment requiring the use of oxygen In the very young regardless of what remedial medical or surgical measures are used death frequently supervenes in serious cases Useless annoying and exhausting cough may require the use of an anodyne in suitable dosage The best way to control cough is with codeine in ¼ or ½ grain (15 to 30 mg)

doses The codeine may be incorporated into a palatable cough syrup or administered in tablet form *Cough must not be suppressed* entirely because coughing is necessary to expel the accumulating bronchial secretions Complete suppression of cough *or the use* of belladonna derivatives is fraught with danger The retained or inspissated sputum may cause atelectasis

The use of sulfa drugs or antibiotics is rarely indicated In the presence of an over whelming infection or debility, however, one or both of these remedial agents should be used in adequate dosage Systemic adminis tration of chemotherapeutic or antibiotic agents frequently fails Troches as a rule have only psychic value Aerosol therapy is the best approach to the effective treatment of acute tracheobronchitis (A complete discus sion of this form of therapy will be found in the section on Chronic Bronchitis and Bronchiectasis)

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SANDY B CARTER

CHRONIC BRONCHITIS AND BRONCHIECTASIS

The increased utilization of available chemotherapeutic or antibiotic agents and a better understanding of the pathologic phys iology has improved the outlook for patients suffering from chronic bronchitis and bron chiectasis With proper use of the newer drugs, the results achieved in some instances are most encouraging Nevertheless, the treatment of bronchial conditions is still largely symptomatic Both of these diseases are generally secondary manifestations, or complications, of a multitude of local thor acic, distant, or systemic diseases Therefore, in order to prevent entirely, or to modify, the severity of chronic bronchitis and bronchiec *tasis energetic and expectant therapy of* responsible primary diseases is essential In any event, correct identification of the pri *mary disease is* the prerequisite for the suc- cessful therapeutic management of these bronchial disorders when they develop

The clinical results achieved with systemic administration of various chemotherapeutic and antibiotic agents in cases of chronic bronchitis and bronchiectasis have been dis appointing Appreciation of the pathologic alteration of the bronchial mucosa and neighboring pulmonary tissue resulting from *these conditions* explains the usually equivo- cal, or actually unsatisfactory, results ob tained when treatment is confined to the *systemic route Specific* and indicated symp- tomatic drugs administered by the various systemic routes in these instances are unable *to penetrate the resulting pulmonary tissue* barriers in sufficient quantities to establish effective therapeutic levels at the site of in fection This shortcoming accounts for the failure of in vivo results with specific drugs to approach, or to parallel, their demonstra ble antibacterial activity in vitro Topical, as well as systemic, therapy is indicated in order to achieve the expected clinical benefits Again, the results achieved following the use of various sulfa drug preparations by nebu lization or direct bronchoscopic instillation have been discouraging The antibacterial activity of sulfa drugs is inhibited in the presence of purulent exudates Antibiotic agents on the other hand are effective when administered as aerosols

Aerosol Therapy Aerosol antibiotic therapy of chronic bronchitis and bronchiec *tasis may produce truly remarkable* and un anticipated successes Aside from surgical removal of the involved pulmonary tissue in bronchiectasis, it is the most important and effective therapeutic measure in these bron chial disorders

The aerosol solution is delivered by means of a satisfactory nebulizer Many nebulizers and innumerable methods of administration have been devised The writers prefer the Vaponefrin apparatus Although the appa ratus and method of choice are a matter of individual preference, better results and bet ter patient co operation can be obtained with the less complicated technics Even with the simplest apparatus careful education of the *patient as to proper* breathing and the art of self administration is of primary importance As a general rule, we prefer not to exceed a volume of 2 cc or 2 5 cc of the solution to be nebulized at each treatment Larger amounts are apt to be tiring to the patient regardless of the method of administration Other investigators have reported satisfac- tory results with the use of aerosol penicillin prepared as a "dust," but in our experience *liquid aerosol therapy is nevertheless* prefer

tions of patients who are considered suitable candidates for aerosol therapy should be determined before treatment is instituted This can be ascertained quickly by examining a Gram stain of a satisfactory sputum specimen microscopically Although the exact nature of the offending micro organism or organisms may not be ascertained accurately by this method it nevertheless serves to classify the responsible etiologic agent as gram negative or gram positive This information is usually adequate and facilitates the rapid institution of effective therapeutic measures The effect of aerosol therapy on the bronchial infection can then be followed by daily Gram stain examinations of the sputum If the anticipated therapeutic response is not achieved additional bacteriologic studies should be carried out in order to identify specifically the offending micro organism

The nontuberculous pathogens responsible for bronchial infections are generally gram positive and will usually respond to aerosol penicillin therapy Occasionally after the gram positive organism is eradicated the bacterial flora will undergo a relative and an absolute increase in both the variety and number of gram negative bacteria Although these organisms are commonly considered to be nonpathogenic as secondary invaders they are unquestionably responsible in many instances for a protracted period of disability

50 000 units (0 5 gm) to 100 000 units (1 0 gm) per cubic centimeter Normal saline is used in preference to distilled water as a solvent for either of these or other, antibiotic agents It is the authors opinion that normal saline is less irritating to the mucous membranes than distilled water Some patients develop a sensitivity to penicillin or streptomycin or both Unless the allergic manifestations are alarming treatment is continued with the assistance of one of the antihistaminic drugs

In the absence of any of the acknowledged contraindications a suitable sympathomimetic agent should be added to the aerosol solution in order to relieve bronchial edema and spasm Frequently, the disturbing clinical symptoms which accompany these pathologic changes in the bronchi either disappear completely or are markedly diminished When edema and spasm are marked the use of 0 5 cc to 1 cc of inhalation adrenalin (1 100) in the aerosol solution may be necessary to achieve the desired results When sympathomimetic drugs are not indicated one minim of 2 per cent tyrothricin solution per cubic centimeter of aerosol solution provides a safe and effective concentration Tyrothricin usually prevents the rapid multiplication of gram negative bacteria and precludes the use of supplementary streptomycin It is not only a valuable prophylactic measure clinically but also tends to preserve the patient s economy The use of a satisfactory antihistaminic in the aerosol solution produces many of the desirable effects which result from the administration of sympathomimetic drugs

bacteria it becomes necessary to supplement the treatment with streptomycin These two antibiotics used in combination can generally handle all of the more common bronchial infections When streptomycin and penicillin are used simultaneously it is advisable not to use the calcium salt of penicillin with streptomycin sulfate since calcium sulfate is precipitated in this solution and will thus interfere with the mechanical efficiency of the nebulizer The dosage of penicillin employed varies from 25 000 units to 50 000 units per cubic centimeter, and the dosage of streptomycin usually employed varies from

biotic solutions and have observed that the incidence of local pulmonary and other allergic reactions is noticeably diminished This advantage may justify the routine use

cubic centimeter) is effective In addition to producing the desirable effects of the sympathomimetic drugs it also acts as a satisfactory expectorant Annoying, useless cough is accordingly converted to a productive non

exhausting cough In cases of allergic bronchitis, the use of aerosol benadryl results in dramatic clinical improvement Those cases which fail to respond to systemic administration of antihistaminics are benefited by aerosol administration Varying concentrations of penicillin, *tyrothricin, streptomycin, adrena*lin and benadryl in the desired amounts may be administered in the same aerosol solution

Aerosol antibiotic therapy should be continued until the maximal beneficial response has been achieved The number of daily treatments and the dosage of the antibiotic agent depend on the nature and severity of the illness and should be adjusted frequently to parallel the clinical and laboratory response The chest roentgenogram should not be used as a barometer of therapeutic response since it does not necessarily parallel the clinical progress of the disease Initially, the more serious cases may require four daily treatments In the presence of concomitant sinus infections which so frequently complicate the picture of chronic bronchitis and bronchiectasis aerosol therapy by the nasal route should be carried on simultaneously Both areas of infection must be controlled in *order to obtain satisfactory results* Lingering infection in either area predisposes to infection of the other The frequent association of sinusitis and chronic bronchitis has justified the existence of the descriptive term *bronchosinusitis*

The intelligent use of aerosol antibiotic therapy in cases of chronic bronchitis due to infection will achieve not only striking palliative results but in many instances, lasting cures Systemic antibiotic therapy is unnecessary and useless once the extrapulmonary manifestations of the primary *disease are controlled* The therapeutic management of the case may then be confined to the aerosol route Aerosol therapy does not cure bronchiectasis It affords effective symptomatic relief and is additionally valuable in the preoperative preparation of these patients for surgical excision of the involved pulmonary tissue Furthermore, many patients who, in the past would have been denied the benefits of surgical therapy because of their debilitated condition, may now be converted into suitable candidates for surgery *Aerosol antibiotic* therapy of pseudobronchiectasis generally results in permanent cures

Although this presentation primarily stresses the benefits of penicillin and strepto*mycin aerosol therapy, it is important to* note that many other drugs can be prepared *for use in this manner* As newer antibiotic agents are discovered and made available many of them will undoubtedly find an important place in this form of therapy Although certain sulfa preparations are quite suitable for aerosol administration the results are generally disappointing Iodide preparations may be administered by the aerosol route for fungous infections of the bronchi In the treatment of bronchial infec

frequently assumes pathogenic qualities or is at least responsible for protraction of the illness This complication may be combated with aerosol iodide therapy To achieve maximal clinical benefits from aerosol antibiotic therapy, the bacterial flora of the sputum should be carefully followed A changing picture requires immediate modification of the therapeutic regimen The management *of each case must be integrated with the* clinical signs and symptoms and laboratory findings The possible and unpredictable variations in each disease and in each patient are impressive

consideration and indicated utilization of other specific supportive, and symptomatic measures Adequate control of exhausting cough may require the administration of small doses of anodynes such as 30 mg of codeine, or 15 mg of morphine Whenever possible, suppression of the cough reflex should be attempted only after the correct diagnosis is established Injudicious symptomatic therapy frequently masks the clinical picture of serious pulmonary diseases and lulls the patient and physician into a feeling of false security Barbiturates and bromides are also effective *in suppressing the cough* reflex When cough interferes with rest and sleep, the use of a suitable sedative or anodyne preparation is indicated One-fourth to ½ grain (15 to 30 mg) doses of

codeine are effective in the suppression of annoying coughs The desirable clinical effects of codeine may be obtained following the administration of 1 or 2 teaspoonfuls of elixir of terpin hydrate with codeine (N F) This popular preparation supplies the added expectorant properties of terpin hydrate Derivatives of belladonna should never be used to control cough or to diminish bronchial secretions When useless cough results from the presence of tenacious sputum, the employment of expectorant drugs is indicated Treatment with expectorant drugs is wholly symptomatic Their usage dates back to antiquity Of the many sedative and stimulant expectorant drugs ammonium chloride ammonium carbonate, potassium citrate, potassium acetate, potassium iodide sodium iodide, syrup of ipecac, creosote oil of eucalyptus oil of turpentine syrup of hydriodic acid and terpin hydrate are the most popular Inhalation of 5 to 10 per cent carbon dioxide for 5 to 10 minutes is an

[illegible]

pectorant qualities of the old fashioned croup kettle should never be underrated It is safe and effective The author has obtained satisfactory results with the following expectorant mixture

Ammonium chloride	ʒvss
Compound mixture of opium and Glycyrrhiza (N F) (brown mixture)	ʒiv

Two teaspoonfuls of this mixture are prescribed four times daily In order to avoid the unpleasant side reactions, especially nausea and vomiting it should be taken after meals and at bedtime The addition of fruit juices makes the prescription more palatable For sedative effects a barbiturate may be added In cases with marked bronchial edema and spasm a sympathomimetic drug may also be added to this mixture The simultaneous use of a suitable antihistaminic as a part of this mixture, or separately, is a desirable practice especially in cases of allergic bronchitis Patients who cannot tolerate ammonium chloride and brown mixture in the recommended dosage should be tried on smaller doses or treated with one of the other expectorants The intelligent use of a satisfactory expectorant, although only symptomatic, is essential in the treatment of chronic bronchitis and bronchiectasis Its value is twofold By making the bronchial secretions more watery, it helps to abolish useless and exhausting cough Likewise, effective expectoration of bronchial secretions permits aerosolized drugs to reach the most remote recesses of the bronchial tree In order to avoid the possibility of accompanying secondary infection with Candida, the initial administration of an iodide may be indicated in conjunction with aerosol antibiotic therapy After the maximal beneficial results of expectorant drugs or mixtures are obtained their continued administration is not only unnecessary but may actually mask and aggravate the clinical picture

Other Therapeutic Procedures In the management of bronchiectasis, *postural drainage* should never be neglected The proper position can be determined after bronchography To derive satisfactory results from this form of symptomatic therapy, the patient should be carefully instructed in the correct performance of this procedure For the first few days careful personal supervision by the physician or trained assistant is necessary Special postural drainage beds are available The instillation of lipiodol into the bronchial tree and bronchoscopic aspiration of tenacious secretions have their merit, but the resulting benefits are temporary These practices are no longer popular forms of therapy Bronchoscopic aspiration during a course of aerosol therapy, however, is helpful and facilitates the achievement of maximal symptomatic relief Crushing of the phrenic nerve, the production of artificial pneumothorax and thoracoplasty have all been tried and recommended in the treatment of bronchiectasis Only in the presence

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maximal symptomatic relief Crushing of the phrenic nerve the production of artificial pneumothorax and thoracoplasty have all been tried and recommended in the treatment of bronchiectasis Only in the presence of uncontrollable hemorrhage should artificial pneumothorax be considered Fortunately massive hemorrhage due to bronchiectasis is uncommon None of these measures however deserves serious consideration Bismuth and arsenic should be used only in the [illegible]

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suitable candidates for surgery should be given the benefit of segmental resection lobectomy or pneumonectomy Excision of all the infected tissue is the only way to cure bronchiectasis Nevertheless the best treatment of bronchiectasis is prevention of the disease When physicians become familiar with its causes and pathogenesis this goal may be approached

In the treatment of chronic bronchitis and bronchiectasis roentgen therapy has proved of some benefit in selected cases Chronic cough which results from the mechanical effect of endothoracic tumors may be relieved by roentgen therapy if the tissue is radiosensitive In selected cases autogenous bacterial vaccines of other responsible al

sults achieved in chronic bronchitis are permanent Stock house dust vaccines are not so effective as dust vaccines prepared from the patient s own home Vaccines may likewise be prepared from the patient s mattress and pillow stuffing Only too frequently desensitization fails to accomplish its intended purpose Some patients may be benefited by removal to a warm dry climate If extrinsic allergens have a role in the disease it may be possible to relocate in a geographic area free of the offending agent or agents Chronic bronchitis due to irritating chemical or physical agents can best be treated by proper prophylaxis or avoidance of the noxious agent No patient who suffers from chronic bronchitis or bronchiectasis should be permitted to smoke Abandonment of this habit will yield gratifying symptomatic relief in bronchiectasis and may result in permanent cures in chronic bronchitis Patients with bronchial disorders should meticulously avoid sudden temperature changes and unnecessary exposure to inclement weather The treatment of psychogenic cough is an exasperating problem in therapeutics willingly consigned to the psychiatrist

In the management of chronic bronchitis and bronchiectasis careful attention should be given to the patient s general condition Unless the general condition is improved and maintained at a satisfactory level all forms of treatment may be in vain A high caloric, well balanced diet should be prescribed The use of supplementary vitamins should be considered and is frequently indicated Debilitated patients may require whole blood transfusions or intravenous amino acids Absolute bed rest is rarely necessary except during febrile periods Plenty of sunshine and fresh air are important Chronic infections of the upper respiratory tract should be eliminated by either medical or surgical treatment As long as there is any infection in the upper respiratory tract recurrence of bronchial disorders may be expected with monotonous regularity Chronic bronchitis is often associated with cardiac decompensation and will be cured or markedly improved by improvement in the card ac status

Although the specific supportive and symptomatic therapy of chronic bronchitis and bronchiectasis has improved the suc-

LOUIS L FRIEDMAN
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DISEASES OF THE LUNGS

EMPHYSEMA

The treatment of emphysema is entirely symptomatic Relief of dyspnea and especially severe paroxysms of dyspnea is the major problem in the treatment of emphysema The most one can expect from presently available and popular therapeutic measures is temporary relief of the clinical symptoms No lasting benefits should be expected Successful treatment of primary diseases capable of producing emphysema is the best safeguard against its development.

Many cases of emphysema develop in asthmatic individuals In these instances the effective management of the asthma will have a beneficial effect on the clinical manifestations of emphysema The use of appropriate vaccines to desensitize these patients

is frequently quite effective in either diminishing or actually eliminating the allergic reactions More recently in cases of emphysema associated with an allergic component the use of various antihistaminic preparations has proved successful To obtain the maximal therapeutic benefits from the use of these new drugs administration should be by the aerosol route (see section on Chronic Bronchitis and Bronchiectasis) Especially in long standing cases systemic therapy is prone to result in failure Aerosol antihistaminic therapy is capable of achieving the desired results both in cases with an allergic component and frequently in those due to other causes Seven and one half grains (0 5 gm) of aminophylline administered in a 20 cc solution is likewise effective in relieving dyspnea associated with emphysema The use of aminophylline by mouth is not as effective chiefly because the large dosage required by this route of administration is nauseating and cannot be tolerated by most patients Results achieved with rectal suppositories of aminophylline 7½ grains (0 5 gm) are likewise discouraging Some proprietary preparations contain a barbiturate in one form or another The relief obtained with these combinations is probably due to the effect of the sedative Properly prepared solutions of aminophylline are likewise effective by the aerosol route Severe paroxysms of dyspnea may require the administration of oxygen Some authorities on the subject of emphysema believe that a mixture of helium and oxygen therapy is more effective Nevertheless the relief obtained with oxygen therapy is not only striking but frequently quite lasting

The use of a sympathomimetic drug such as ephedrine sulfate ⅜ to ⅝ grains several times daily is generally effective In the absence of acknowledged contraindications this drug may be administered to advantage Likewise 1 cc of adrenalin in oil (1 500) given intramuscularly from one to three times daily [illegible]

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preparations is indicated One half to 1 cc of [illegible]

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of aerosol adrenalin (1 100) Unfortunately the administration of these drugs in sufficient dosage to achieve the desired therapeutic benefits predisposes to annoying side reactions Insomnia and tachycardia are only a few of the more undesirable side effects The routine use of a sedative drug should be the rule when large doses of sympathomimetic drugs are used In this manner the clinical manifestations of the undesirable side reactions may be masked Many varieties of sympathomimetic agents are available Any one of these preparations can be used with equal benefit Undesirable side reactions occur with all of these drugs when clinically effective amounts are prescribed Pharmaceutical companies have tried in vain to eliminate these annoying complications Sympathomimetic drugs should not be used continuously for more than brief periods of time Prolonged use of these agents eventually renders the patient resistant to their beneficial pharmacologic actions The prolonged use of aminophylline is attendant with the same limitations The best results will be accomplished by varying the drugs used and the route of administration

In acute episodes of dyspnea the use of a barbiturate a bromide or any other satisfactory sedative in adequate amounts to relieve the omnipresent apprehension of the patient is imperative This is an important admonition since this undesirable psychogenic reaction aggravates all of the clinical symptoms especially dyspnea The use of morphine and other opiates is contraindicated in patients whose emphysema complicates asthma

Variable results may be obtained with the use of abdominal binders as described by Alexander Kountz and Kerr They are prescribed on the assumption that dyspnea may be relieved by increasing the intra abdominal pressure Many patients cannot tolerate these belts and readily forego the possible symptomatic benefits Abdominal belts should be recommended however only after fluoroscopic examination has ascertained the degree of diaphragmatic mobility The prevention and effective treatment of bronchitis are of utmost importance in the therapeutic management of emphysema A combination of benadryl adrenalin penicillin and streptomycin or tyrothricin administered by the aerosol route is exceptionally effective when

emphysema and chronic bronchitis coexist A more detailed discussion of this phase of the t
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Bronchiectasis Regardless of the various therapeutic measures in emphysema, the ultimate prognosis is poor

Louis L Friedman
Sandy B Carter

PULMONARY FIBROSIS

Pulmonary fibrosis may result from any *acute or chronic disease of the pleura or* bronchopulmonary tissue With the onset of symptoms due to fibrosis of pulmonary tissue the severity of the disease is usually progressive There is no effective therapy for this condition Therapeutic measures are capable of effecting only temporary symptomatic relief The most frequent clinical manifestations of the disease are chronic cough, foul sputum cyanosis dyspnea and recurrent bronchopulmonary infections Management of the disease depends entirely on the nature of the prevailing clinical symptoms and their severity Systemic administration of the various chemotherapeutic and antibiotic agents is ineffectual Destruction of the normal pulmonary architecture, especially the vascular network, is responsible for this failure The best results are obtained from the use of *indicated aerosol therapy This therapeutic* measure, although only palliative affords effective relief of annoying symptoms The ultimate survival prognosis is influenced favorably by the use of aerosol antibiotics for the control of secondary infections Bronchial infections and dyspnea will respond to the measures described in the sections on Chronic Bronchitis, and Bronchiectasis and Emphysema, respectively

Likewise, the same general supportive and symptomatic considerations are applicable in this condition Every effort should be made to prevent secondary infection and to maintain a satisfactory state of general health Pulmonary fibrosis, however, is more apt to result in *heart failure than either chronic* bronchitis or bronchiectasis When this complication develops, the usual methods of *restoring* and maintaining the failing cardiac reserve are indicated Since the treatment of pulmonary fibrosis is so unsatisfactory, best approach to the problem appears to energetic and effective therapeutic manag ment of the primary diseases from which may develop

Louis L Friedma
Sandy B Carter

COLLAPSE OF THE LUNG, ATELECTASI

The rational and successful treatment pulmonary collapse depends on rapid ac rate determination of the cause and ext of the collapse The principles of prevent

hand, will *vary according to the type a* the cause Pulmonary collapse is divided i two main types, simple and massive If t collapse is limited to a few alveoli or lobul it is termed simple Massive collapse i cludes the more extensive cases in whi there is involvement of one or more lobes even a complete lung This classification co siders merely the amount of pulmonary tiss involved, but it can be readily appreciat that massive collapse will call for mo energetic measures than collapse of a fe alveoli or lobules The treatment of pulm nary collapse will be more *effective* if t cause of the collapse is known For instanc treatment would be different in cases due *compression from pleural effusion* or spo taneous pneumothorax from those due obstruction of the bronchi or bronchiole The same etiologic factor may be respo sible for either simple or massive collaps depending entirely on the amount of pu monary tissue involved

Pulmonary collapse is usually the resu of occlusion of one or more bronchi bronchioles The most frequent cause such obstruction is the presence of *som* condition which produces an increase bronchopulmonary secretions combined wit *interference of the cough reflex* Chemic

sociated with complicating atelectasis ar surgical procedures and trauma Preoperativ and postoperative sedatives and analgesics anesthetic agents, shock, nervous factors, and

aspirated material all predispose to this serious complication Other causes of atelectasis include pulmonary embolism infarction tumor allergy and extrapulmonary pressure

The three important considerations in the treatment of pulmonary collapse are prevention removal of the endobronchial obstruction and attention to the secondary results of atelectasis In many patients particularly those with simple collapse treatment is seldom required and the atelectasis is frequently overlooked clinically The reason for this is that a large number of postoperative patients suffering from atelectasis will unintentionally clear the secretions from the bronchi and re-expand the collapsed portion of the lung by reflex deep breathing and coughing There are numerous prophylactic measures that should be observed especially in patients who from past experience are known to be more susceptible to pulmonary collapse such as the aged the very young the debilitated the postoperative patient (particularly after abdominal or thoracic surgery) and those who have been victims of serious traumatic injuries Operations should be postponed for two or three weeks following infections of the mouth and respiratory tract because of the increased danger of accumulating tenacious secretions The choice of anesthetic and preoperative and postoperative medications plays some part For instance ether irritates the bronchial mucous membrane and causes increased secretion as compared with various gases

reflex bronchoconstriction and to diminish bronchial secretions by the use of atropine The cough reflex is restricted by pain and suppressed by opiates Judicious use of only minimal amounts of opiates is therefore recommended Smoking irritates the respiratory tract and should be forbidden in the immediate postoperative period The bronchial secretions are made more serous by humidification of the air and by the use of iodides and alkalis Patients should not be exposed to chilling or drafts Aspiration of vomitus saliva and mucus should be prevented by the use of suction when indicated or by proper postural position In the immediate postoperative period after all major surgical procedures and regardless of the anesthetic used a mixture of oxygen (90 per cent) and carbon dioxide (10 per cent) should be administered routinely for 5 to 10 minute periods at regular frequent intervals The use of deep breathing exercises frequent changes of position avoidance of deep narcotization and of tight thoracic and abdominal binders are other recommended prophylactic measures Discreet early ambulation increases pulmonary activity and consequently, prevents accumulation of secretions It is to be emphasized that the cough reflex must be encouraged and not suppressed Careful nursing is important in both the prophylaxis and treatment of atelectasis From experience gleaned in other conditions we feel that parenteral and aerosol antihistaminics may be of real prophylactic and possibly therapeutic value

The treatment of pulmonary collapse is both symptomatic and specific Control of pain and dyspnea may be accomplished with the use of a suitable sedative in adequate dosage Barbiturates and bromides are popular If these are found to be inadequate the use of oxygen and an opiate such as mor

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mg) to ¼ grain (15 mg) doses hypodermically may be required to relieve pain and dyspnea This may be repeated as often as necessary if the respiration remains 16 per minute or over Cheyne Stokes breathing must always be avoided A sitting or semi sitting position will usually be more comfortable Breathing a mixture of 90 per cent oxygen and 10 per cent carbon dioxide for 5 to 10 minutes every hour will stimulate respiratory rate and depth and produce more watery secretions This practice is more effective in prophylaxis than in treatment Fluid balance must be maintained during the emergency until the patient is able to satisfy his own requirements

In most cases of significant pulmonary collapse there is an endobronchial obstruction which demands immediate removal. It is necessary that the bronchi be cleared within a few hours after the development of

atelectasis if complete and rapid re expansion is to be achieved If the obstruction is due to reflex bronchial *spasm, good results may* be obtained with the intravenous injection of ¹⁄₁₀₀ grain of atropine sulfate or 1 grain of papaverine hydrochloride The use of *intravenous aminophylline and* calcium glu conate may be of some value Sym pathomimetic drugs are likewise frequently beneficial If the simpler measures such as postural drainage are not effective, intra bronchial catheterization with subsequent aspiration or bronchoscopic aspiration may be necessary Postural drainage is accom plished by placing the patient in a position with the involved lung uppermost Retained secretions will gravitate downward stimulate the mucosa and the resulting cough may be sufficient to expel the obstructive material Occasionally, when conditions permit, a moderate fistic assault on the thorax by the physician or a rather intense shaking of the patient will result in relief of the obstruction This practice is not recommended routinely Intrabronchial catheter aspiration can be used to remove aspirated vomitus mucus, and saliva This can be done at the bedside By turning the patient from side to side, the catheter can be passed into each bronchus and suction applied Some feel that blind suction by catheter may cause serious damage by its traumatic effects In the ab sence of a competent bronchoscopist, however, intrabronchial catheter aspiration assumes a prominent role in the treatment of atelectasis Suction drainage under direct vision of the bronchoscope is, nevertheless *the most efficient and least traumatic type of aspiration* It offers visual assurance that the main bronchi have been cleared Further more it assures adequate suction without trauma *and provides an opportunity to apply* shrinking solutions to areas of edema

Bronchoscopy is particularly valuable in (1) postoperative patients who through pain or debility are *unable to remove obstructing* secretions from the bronchi, (2) unconscious patients and those who have suffered injury to the nervous mechanism controlling the cough reflex, *such as occurs in lesions* of the cervical portion of the spinal cord or in juries to the midbrain, (3) patients with injuries involving the airway with aspiration of blood or other *foreign material*

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the relief of pain and dyspnea, can frequently be obtained by artificial pneumothorax Enough air is introduced into the pleural space on the side of the collapse to restore the intrapleural pressure to a normal nega tive reading It must be remembered how ever, that any offending obstruction must be removed before re expansion of the lung will take place

The secondary results of atelectasis must be considered because of the omnipresent danger of infection particularly broncho pneumonia The drug of choice in most cases is penicillin which can be administered parenterally Aerosol therapy is useful in bronchial infections (see section on Chronic Bronchitis and Bronchiectasis) A single daily injection of 300,000 units of one of the long acting penicillin preparations is adequate The choice of a chemotherapeutic and anti biotic agent and the route of administration all depend on the nature of the infection and therapeutic response

In summary, the treatment of pulmonary collapse consists of prophylactic measures actual treatment, and attention to the sec ondary results The most effective prophylac tic measures are those which prevent respiratory tract infections, excessive bron chial secretion, and stimulate the cough re flex *In treatment, removal* of the offending endobronchial obstruction is the main con sideration, and bronchoscopy is the method of choice if simpler measures are not effec tive. *Secondary infection* is usually best managed by the use of penicillin

LOUIS L FRIEDMAN
SANDY B CARTER

PULMONARY EMBOLISM

It was formerly believed that pulmonary embolism was invariably the sequel either of abdominal or pelvic operations or of injuries such as fracture of the hip It is now known that pulmonary embolism is often a compli cation of any condition, surgical or medical, in the treatment of which the patient is neces sarily confined to bed or immobilized for prolonged periods of time Any chronic, de bilitating disease, particularly in the aged

and asthenic, may be complicated by pulmonary embolism Into this category would fall such conditions as inoperable tumor, cerebral vascular accident, paralysis from any cause, marked malnutrition, and advanced senility Trauma of the vascular system may produce thrombus formation and subsequent embolism In recent years, considerable stress has been placed on thromboembolic phenomena following myocardial infarction However, in spite of the more frequent recognition of thrombo embolic complications in medical patients, they are still most often encountered in postoperative and traumatic states Why does thromboembolism occur in these postoperative, traumatized, and bedridden patients? It has been postulated that, following surgical procedures and trauma, a substance is liberated which increases blood viscosity and the tendency to intravascular clotting Of prime importance, however, is the slowing of circulation and stasis which occur when prolonged bed rest becomes necessary While the patient is at rest there is a physiologic decrease in cardiac activity and subsequent slowing of the circulation During normal activity blood flow through the lower extremities is assisted by muscular contraction and pressure on the veins which forces blood back toward the heart Deep breathing, resulting from unusual physical activity, produces an increase in intrapleural negative pressure which helps to maintain an adequate circulatory rate Any interference with circulation, either by diminution of the normal physiologic forces or by mechanical obstruction of the venous return, may lead to stasis and subsequent thrombus formation Most attention in the prevention and treatment of pulmonary embolism is focused on the lower extremities *The reason for this is that the most common* site of phlebothrombosis, subsequent to interference with circulation, is in the deep veins of the leg, and most cases of pulmonary embolism are secondary to phlebothrombosis of these veins

Prophylaxis Therapy of pulmonary embolism is both prophylactic and specific Until recent years therapeutic measures were almost entirely symptomatic Within the span of a few years three advances have been made in the treatment of pulmonary embolism These are ligation of the involved veins, early ambulation following major surgical procedures, and anticoagulant therapy Al-

prevention is maintenance of adequate circulation Patients who must remain in bed,

must be done even at the risk of alarming the patient Mental discomfort is still preferable to a serious illness or possible death The patient or trained attendant should be instructed in the use of preventive measures

knees partially flexed by a supporting pillow or by folding the hospital bed is recommended frequently for the comfort of the

sure on the veins and interferes with the return of the blood from the lower extremities

The patient must be instructed in appropriate muscle exercises of the lower extremity At least three times daily the patient should observe a regular exercise period consisting

tendant should passively exercise the extremities Another way to increase muscle tone of the lower extremities is to elevate the head of the bed about 6 inches In order to avoid *sliding* downward, the patient pushes against a well positioned footboard This produces the desired exercise effect Deep breathing exercises are also required at regular intervals Six to ten forced inspirations and expirations every hour or so are effective There has been a great reduction in the incidence of pulmonary embolism since the institution of early ambulation following major surgery, childbirth, hip fractures, etc The activity of ambulation maintains circulation By ambulation is meant active walking and exercise and not merely sitting in a wheelchair The

latter is a dangerous practice because of the pressure on the vessels from the flexed joints Other prophylactic measures include prevention of shock avoidance of hemoconcentration and maintenance of cardiac output

Finally prophylaxis includes venous ligation and anticoagulant drugs When used in the treatment of pulmonary embolism these procedures are really prophylactic steps to prevent additional and possibly fatal emboli

develop this condition and of preventing recurrent pulmonary embolism in patients who have already experienced a nonfatal episode of embolism In elderly patients who are confined to bed or must undergo major surgery venous ligation is often recommended before or at the time of operation This will prevent emboli from anticipated phlebothrombosis of the deep leg veins The same step is often taken in the presence of hip fractures in the aged Following myocardial infarction dicumarol is recommended in the majority of cases until activity is resumed This is primarily intended to prevent the development of phlebothrombosis of the deep leg veins to prevent extension of the thrombus in the coronary arteries and to prevent the development of a mural thrombus

Active Treatment Once pulmonary embolism has occurred it must be treated heroically energetically and without procrastination Every effort must be exerted to prevent additional thrombo embolic phenomena Prevention is the most effective form of

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should be given intravenously to relieve the pain Morphine or some other suitable nar

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(90 mg) of papaverine hydrochloride and 1/150 grain of atropine sulfate administered hypodermically are recommended for the relief of reflex vascular and bronchial spasm Papaverine and atropine should be administered hypodermically for several days at 4 hour intervals but after the emergency has passed oral administration will suffice

For relief of dyspnea oxygen should be administered by nasal catheter mask or tent If shock supervenes it must be combated with the measures already outlined above and by cautious infusions of whole blood or plasma The results of embolectomy in pulmonary embolism are discouraging and the procedure as a rule fails to achieve its therapeutic goal Occasionally a rare success is reported from institutions with well organized "embolectomy teams

When a patient has recovered from pulmonary embolism the major problem is the prevention of a second episode which may prove fatal Both venous ligation and anticoagulants have their proponents Ligation will only prevent emboli from sources distal to the ligation whereas anticoagulants usually prevent additional thrombosis throughout the body Ligation of veins is superior

emboli from the leg veins are difficult to prevent with anticoagulants since they occur at irregular and unpredictable intervals Venous ligation is also the treatment of choice when anticoagulants are contraindicated and when they are ineffective In the majority of cases anticoagulant therapy is preferable To be effective venous ligation must be proximal to the thrombus When the thrombus is in the plantar or deep leg veins superficial femoral vein ligation distal to the profunda is recommended If the thrombus is higher it may necessitate ligation of the common femoral vein common iliac vein or even the inferior vena cava Each of these vessels has been ligated successfully but the higher the ligation the more difficult the procedure and the less likely the development of subsequent adequate collateral circulation

The anticoagulants heparin and dicumarol are most often used for the prevention of original or recurrent pulmonary embolism. When the possibility of thrombo embolic phenomena is recognized early dicumarol alone is usually adequate because an effective reduction of prothrombin concentration can be accomplished before the danger becomes manifest On the other hand when pulmonary embolism has already occurred a rapid anticoagulant effect must be obtained The combined use of fast acting heparin as well

blood dyscrasias with bleeding tendencies, ulcerative lesions or open wounds, and recent operations on the brain and spinal cord If for any reason the anticoagulant effect be comes undesirable or dangerous, heparin can be neutralized by intravenous protamine or the hypoprothrombinemia produced by dicumarol usually can be raised to a safe level by the repeated intravenous use of large doses of vitamin K or vitamin K oxide and whole blood transfusions Donors, previously prepared with large doses of vitamin K, are preferable if available Before anticoagulant therapy is instituted a prothrombin concen tration is determined Fifty milligrams of heparin are then injected intravenously every 4 hours until the slowly acting dicumarol produces the desired reduction in prothrombin concentration to a level 30 to 50 per cent of normal Heparin should then be discontinued There are other ways of giving heparin but this is the most convenient

Unless alarming, febrile reactions to heparin may be ignored At the same time that heparin therapy is started, a single dose of 300 mg of dicumarol is given by mouth On each subsequent day of therapy, a pro thrombin concentration is determined on blood obtained at least 3 hours after heparin injection for as long as it is used On those days that the prothrombin level is above 30 per cent, 200 mg of dicumarol are given If the prothrombin concentration is below 30 per cent, no dicumarol is given An average dose is 200 mg Some patients require more, and others less, depending on the individual response The object of treatment with dicumarol is to maintain the prothrombin concentration between 10 and 30 per cent Some feel that a reduction of prothrombin concentration to 40 or 50 per cent is adequate to prevent thrombo embolic phenomena and the danger of complicating hemorrhage is thereby reduced During anticoagulant therapy, frequent urinalyses and other indicated clinical and laboratory examinations should be performed daily in order to discern the first evidence of a complicating hemorrhagic response

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PNEUMOCONIOSIS

Pneumoconiosis results from the inhalation of certain dusts over a long period of time It is characterized by the development of proliferative and fibrotic changes in the lungs The most important dust diseases of the lung are anthracosis, asbestosis, and silicosis

Anthracosis (coal miner's lung) is rarely associated with any significant impairment of health or with physical disability It is felt that advanced anthracosis is not only unrelated to the development of tuberculosis but may actually prevent this disease Anthracosis, however, renders the individual more susceptible to pneumonia The major prob lem in connection with anthracosis is the prevention of infection Uncomplicated an thracosis requires no treatment unless it pro duces an unusual degree of pulmonary fibrosis

Asbestosis is a form of silicosis which results from the inhalation of asbestos dust This dust is primarily composed of mag nesium silicate Its association with pulmo nary tuberculosis is not common The condi tion predisposes to chronic bronchitis, bron chiectasis, emphysema, and bronchopneu monia The treatment of these conditions is discussed above Since there is no treatment for asbestosis, suitable and necessary pro phylactic measures designed to prevent its development should be instituted during the processing of asbestos from the crushed mineral

Of the dust diseases, *silicosis* is the most

value of aluminum dust in silicosis Insufficient time has elapsed to evaluate *this meas-* [illegible]

peutically The prophylactic use of aluminum dusting will require more investigation be*fore it is accepted* or rejected It has some serious drawbacks Large concentrations of aluminum powder exert a harmful effect on cases of active or inactive pulmonary tuberculosis Furthermore, its routine adoption in industries with a silicosis hazard may pre-

dispose to relaxation of proved and effective prophylactic measures

As in asbestosis, since there is no treatment for silicosis, prevention of the disease deserves special attention It is the responsibility of industry to institute proper prophylactic measures in all occupations associated with a silicosis hazard In addition employees should be made familiar with the risks involved and educated in the maintenance of satisfactory prophylactic standards A competent sanitary engineer should be employed to supervise the program of prophylaxis in all industries with a silica hazard With the use of such instruments as the Greenburg Smith impinger, the electrostatic precipitator, the konometer, and the Owens jet, the total number and size of the silica particles can be determined When the limits of the safety are exceeded, suitable prophylactic measures should be instituted immediately Up to 5 000 000 particles of silica dust per cubic foot is considered a safe concentration

Proper prophylaxis depends on the use of good housekeeping proper ventilation and wet methods The use of specially devised respirators is effective Many workers, however would rather chance the ultimate consequences of prolonged exposure to silica than wear the respirators There are several methods of employing water or other liquids prophylactically Water may be used to suppress dust at its origin as in wet drilling It may be used as a spray to remove the hazardous dust from the air Redispersion of the dust may be prevented by keeping all walls, floors, and other surfaces wet In order to be effective this measure must be practiced without relaxation Frequent, regular determinations of the effectiveness of the selected safeguard are necessary in order to insure proper prophylactic control On the surface, the financial expenditure involved in providing safe places of employment may appear formidable, impossible, and economically unsound In actual practice, however, proper prophylaxis pays added dividends to the employer while safeguarding the health of the employee Only rarely is it impossible to control the silica hazard

Pre-employment roentgen examinations of the chest should be a routine requirement before engaging an employee for an occu [illegible] evidence of any pulmonary disease especially active or inactive tuberculosis, should never be employed Likewise, the employment of positive tuberculin reactors should be avoided Inhaled silica has a deleterious effect on pulmonary tuberculosis Follow up roentgen studies are the only means of detecting silicosis in its earliest stages As soon as evidence of silicosis is detected in the roentgenogram, the employee should be transferred to an occupation free of silica dust When this precaution is observed, the incidence of disabling and advanced silicosis may be expected to decline It is important to recognize silicosis in the asymptomatic stage When clinical symptoms develop the course of the disease is usually progressive Of added importance is the fact that silicosis predisposes to pulmonary tuberculosis This complication occurs by various estimates, in from 65 to 95 per cent of the cases The development of silicotuberculosis heralds a fatal outcome It is the most serious complication of silicosis and, with rare exception, is refractory to all forms of available tuberculosis therapy

Chronic bronchitis, bronchiectasis, emphysema, and pulmonary infections regularly complicate silicosis The treatment of these secondary conditions is outlined under the respective sections dealing with these diseases Again it must be stressed that aerosol therapy with various chemotherapeutic and antibiotic agents is preferable to systemic administration General supportive and symptomatic measures are essentially the same as for other bronchopulmonary diseases

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PULMONARY ABSCESS

Many pulmonary abscesses heal spontaneously A large number respond to conservative medical management, a few require surgical intervention, and a very small number respond to no treatment at all The intelligent use of sulfa drugs and antibiotic agents in those conditions which may be responsible for the development of a lung abscess has unquestionably reduced the inci

dence of this complication The sulfonamides have greater prophylactic than therapeutic value The antibiotic agents, particularly penicillin, however, exert therapeutic as well as prophylactic effects The prophylactic use of sulfa drugs or antibiotic agents in connection with surgical procedures involving infected areas of the head or neck is mandatory Recent evidence has been accumulated which suggests the prophylactic superiority of the combined use of aerosol antibiotic with the simultaneous administration of a suitable sulfa drug or antibiotic systemically When prophylaxis is limited to the systemic

bility of limiting prophylaxis to the use of aerosol antibiotics is receiving attention at this time, and the early results are encouraging

Although the systemic administration of large doses of indicated antibiotic agents over long periods of time has cured many cases of lung abscess, aerosol antibiotic therapy is the treatment of choice The use of systemic

trolled, aerosol antibiotic therapy may be relied upon to achieve any of the possible therapeutic benefits A complete discussion of aerosol therapy may be found in the section on Chronic Bronchitis and Bronchiectasis Direct bronchoscopic instillation of therapeutic agents into the abscess cavity has its advantages When the bronchus leading to the abscess cavity is blocked by a tenacious exudate, bronchoscopic aspiration and instillation of the indicated antibiotic agent merits serious consideration In the presence of a patent bronchus, bronchoscopic instillation need not be considered since aerosol therapy will achieve at least equal, if not better, results Bronchoscopic instillation of concen

complicating bronchiectasis Choice of a suitable antibiotic agent is determined by the nature of the responsible micro-organism and the general bacterial flora To achieve the best results, the therapeutic benefits of aerosol therapy should be evaluated daily In the treatment of lung abscess, the daily amount and gross characteristics of the sputum are important guides Detailed and specific information can be obtained from bacteriologic studies Frequent roentgen examinations of the chest and daily evaluation of the patient's clinical progress will also reflect the success or failure of the therapeutic

cal and laboratory evidence

The success or failure of aerosol therapy in the treatment of lung abscess depends on the use of other important therapeutic measures Correct postural drainage two or three times daily is absolutely necessary The use of expectorant drugs is useful in maintaining bronchial patency and in relieving useless cough When fusospirochetal organisms are present in large numbers, the use of an arsenical or bismuth may speed recovery Iodides are necessary to eliminate the Candida The use of pneumothorax is dangerous and is mentioned only for condemnation

Phrenic crush, however, may prove helpful Vaccine treatment and roentgen therapy are valueless Amebic abscesses of the lung usually respond to specific amebacidal therapy The drug of choice is emetine hydrochloride or chloroquine One gram of emetine may be administered hypodermically for a period of 10 days This is a dangerous drug and should be used with caution It is contraindicated in patients with myocardial disease Careful evaluation of the cardiac status including, especially, an electrocardiogram should be carried out before during, and after each course of therapy Neuritis is another important toxic effect of emetine Large doses of thiamine chloride should be prescribed when emetine is used

instance in which massive systemic sulfa drug and antibiotic therapy are indicated and imperative

In order to be successful with the medical management of lung abscesses, careful attention must be given to the patient's general condition as well as to the local disease

Frequent blood transfusions are beneficial A high caloric nutritious diet should be prescribed Those patients who suffer from anemia are not only candidates for blood transfusions but should also receive intraveno vitam min (

Well managed aerosol therapy will usually result in the cure of acute lung abscesses and the prevention of most secondary manifestations such as bronchiectasis and fibrosis Although it may be tried in chronic abscesses the results are disappointing Aerosol therapy however should be used in an effort to convert debilitated patients and unfavorable cases into satisfactory surgical risks Surgery should be recommended in all cases which fail to respond to a satisfactory trial with conservative medical therapy Unnecessary procrastination predisposes to a poorer prognosis and further complications The use of aerosol therapy preoperatively and postoperatively will minimize the risk of surgery and the possibility of serious complications Unprejudiced co operation between the internist and surgeon is essential for the successful management of all lung abscesses Following spontaneous resolution medical cures and surgical drainage frequent follow up roentgen examinations are necessary Pulmonary abscesses have a notorious habit of recurring even after months of inactivity and apparent cure

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DISEASES OF THE PLEURA AND PLEURAL CAVITY

ACUTE PLEURISY

Effective symptomatic relief of pain is the first objective in the treatment of pleurisy The generous use of ¼ grain (15 mg) of morphine or ½ grain (30 mg) of codeine is generally necessary to produce the desired analgesia in the early stages of the disease As the inflammatory reaction in the pleura subsides the use of milder analgesics such as acetylsalicylic acid will afford adequate control of pain Disappearance of the patient s apprehension and sense of impending disaster parallels the symptomatic relief of pain The marked improvement in the patient s general condition which accompanies satisfactory analgesia is truly dramatic Immobilization of the affected hemithorax results in added clinical benefits This may be accomplished by strapping the affected side with adhesive tape or application of a tight binder to the entire thorax Proper immobilization requires the application of these restraining devices during full expiration The patient should be instructed to lie on the affected side Additional benefit is obtained by placing a pillow under the involved hemithorax Injection of the intercostal nerves over the area of pleurisy with an anesthetic agent such as procaine cocaine or novocain may also provide effective relief of pain

We feel that the intravenous administration of calcium gluconate often produces satisfactory analgesia in pleuritis Ten cubic centimeters of a 10 per cent solution (1 gm) is the recommended dose The use of a hot water bottle is always comforting Although these measures may have a place in the control of pleuritic pain the use of a satisfactory narcotic is always indicated and imperative The excruciating pain of pleurisy predisposes to voluntary restriction of respiration and frequently results in self produced dyspnea and cyanosis Until adequate relief of pain is accomplished the use of oxygen may be necessary

Only tuberculous pleurisy may be primary This disease is discussed elsewhere in this book All other inflammatory reactions of the pleura are secondary to local thoracic distant or generalized diseases The treatment of pleurisy complicating these primary diseases for which there is no specific therapy is entirely symptomatic Aside from the symptomatic relief of pain dyspnea cyanosis cough and apprehension satisfactory treatment of fibrinous pleuritis depends entirely on the correct therapeutic management of the primary responsible disease Of the multitude of clinical entities which may cause pleurisy relatively few respond to specific drug therapy The widespread use of sulfa drugs and antibiotic agents in the treatment of pulmonary and other infections

has resulted in a diminished incidence of clinical pleurisy

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PLEURISY WITH EFFUSION

Aside from the added problem of fluid in the pleural cavity the treatment of sero fibrinous pleurisy is similar to the manage ment of fibrinous pleurisy As a rule it is inadvisable to aspirate serofibrinous effusions unless the responsible agent is drug sensitive Careless thoracentesis may convert a rela tively harmless serofibrinous effusion into a troublesome empyema In the presence of massive effusions resulting in marked dysp nea thoracentesis is indicated Aspiration of the pleural cavity should be preceded by careful localization of the fluid This can be accomplished with the aid of physical signs roentgen examination in various positions and fluoroscopy *In spite of all possible pre* cautions unsuccessful and traumatic thora centesis may be encountered Even large effusions may be difficult to locate with the

This has the effect of allaying apprehension

event of an untoward reaction

The use of sympathomimetic drugs such as epinephrine hydrochloride in these emer gencies is fraught with danger and is contraindicated

Thoracentesis is best accomplished with the patient in a sitting position A high back rest or the lateral decubitus position may be necessary for those patients who are unable to maintain sitting posture The skin is prop erly sterilized and the patient carefully draped as for a surgical operation Using a small needle the skin at the site of the punc ture is infiltrated with a local anesthetic such as ½ to 1 per cent procaine After infiltration of the skin the needle is introduced deeper into the subcutaneous tissues injecting the anesthetic as the needle is slowly pushed for ward When one is certain that the anesthetic has been introduced as deep as the pleura the small needle is withdrawn A large 18

lower rib in order to avoid injury to the intercostal artery and nerve The needle *should be slowly forced into the pleural cav* ity with great care in order to avoid injury to the underlying lung If a bloody tap oc curs it is wise to withdraw the needle and attempt the aspiration in another location

When one is certain the pleural cavity has been entered careful aspiration with a 20 to 50 cc syringe is attempted One must be

tached to the syringe When the valve is turned one way the fluid from the syringe can be ejected into a suitable container When the valve is turned back more fluid *may then be aspirated from the pleural cav* ity Successful withdrawal of thick exudates is accomplished more easily and safely after normal saline is instilled into the pleural cavity

The intrapleural use of heparin to decrease fibrin formation requires additional investi gation before its utilization can be recom mended Streptokinase may also prove to be of value

There is no definite rule regarding the amount of fluid which may be aspirated It is a good practice to remove all the fluid pos sible before signs of cardiorespiratory dis tress supervene When the patient complains of a "pulling" sensation in the chest dyspnea or coughs slightly thoracentesis must be terminated These symptoms are the result of a too rapid re expansion of the collapsed lung or a shifting mediastinum with consequent torsion of the great vessels at the base of the heart The introduction of a small amount of air will relieve the symptoms and also provide more satisfactory roentgen ray and fluoroscopic localization of the fluid In non tuberculous effusions replacement of the aspirated fluid is contraindicated and should be avoided whenever possible Only in the event of tuberculous pleurisy with demon strable roentgen evidence of underlying pul monary tuberculosis should a pneumothorax be established at the time of thoracentesis

Should pleural adhesions follow resorption of the exudate as they frequently do, the induction of a therapeutic pneumothorax at a future date will be *difficult or impossible* to accomplish Before the aspirating needle is withdrawn 50 000 units of penicillin should be instilled prophylactically in an *effort to prevent secondary infection* To avoid draining sinuses the site of entrance should be massaged briskly, and the patient should be encouraged to lie on the affected side for several hours The latter suggestion may be impossible to observe in the presence of marked dyspnea Subsequent aspirations, if necessary, should be performed at other *sites in order to avoid local complications* When the needle is in place, the patient must never be permitted to move the arm on the ipsilateral side Pulmonary laceration may result or the needle may be broken

If the serofibrinous effusion is due to a penicillin sensitive organism, 50 000 units of this drug may be instilled daily, or twice daily, until the fluid is sterile on seven successive cultures or the effusion is resorbed Once a serofibrinous exudate resorbs, it does not tend to recur The introduction of con

in the pleural cavity, it will act as a diluent for the penicillin Otherwise it is best to dissolve the penicillin in normal saline in such proportions that the resulting solution will not contain more than 500 to 1000 units per cubic centimeter If the organism is penicillin resistant, streptomycin may be substituted As much as 500 000 units may be instilled once or twice daily The con*centrations of streptomycin* should not exceed 10 000 units per cubic centimeter Simultaneous administration of systemic chemotherapeutic and antibiotic agents is necessary to obtain a lasting cure Both penicillin and streptomycin are absorbed from the pleural cavity General drug allergy has been observed after the intrapleural use of these drugs without concomitant or previous administration *To accelerate recovery from* this complication the pleural cavity should be thoroughly washed with a solution of normal saline

Prior to the era of antibiotics, it was the general tendency, for various reasons, to avoid aspiration of both bacterial and nonbacterial serofibrinous pleural exudates unless absolutely necessary Some men still *adhere to this restriction* The intelligent use of indicated antibiotics in bacterial serofibrinous pleural effusions unquestionably prevents the development of a large number of empyemas The satisfying experience with repeated antibiotic instillation and aspiration in indicated cases of bacterial serofibrinous exudates *supports* the continued use of this therapeutic and prophylactic practice All bacterial serofibrinous effusions should be considered potential empyemas and treated accordingly

As regards the treatment of tuberculous effusions the reader is referred to the section on tuberculosis

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LÖFFLER'S SYNDROME

Loffler's syndrome is a nonspecific disease which is characterized by leukocytosis with eosinophilia and transient migratory infiltrations of the pulmonary tissue It is generally *considered to be an allergic pneumonitis* and is most frequently associated with parasitic infestations of the intestinal tract It has been observed in such conditions as ascariasis amebiasis, trichinosis, infestation with Strongyloides, and in other parasitic diseases Patients suffering from asthma allergic rhinitis and urticaria also are known to develop this syndrome The authors observed a case following smallpox immunization in a child Since the disease is *nonspecific* the first step in the treatment of this condition

As a general rule, patients suffering from Loffler's syndrome are not particularly ill. Many of them remain *ambulatory* and, quite often the syndrome is recognized only accidentally in the course of a mass survey or other routine roentgen studies of the chest With the exception of eliminating the responsible allergen, parasite *or otherwise* treatment of Loffler's syndrome is entirely

symptomatic Relief of local pulmonary symptoms such as cough and wheezing may be accomplished by the use of any of the available antihistaminic agents The drug of choice should be administered by systemic route at first If this fails aerosol antihistaminic therapy should be given a trial (see section on Chronic Bronchitis and Bronchiectasis) Evidence is accumulating which indicates that the antihistaminics are of real value in this condition

Bed rest is usually indicated Diet and fluid balance offer no problem because patients generally maintain their usual dietary habits during the illness For restlessness a suitable barbiturate or bromide preparation in required dosage should be prescribed liberally Analgesics and antipyretics are often required for general malaise and fever The symptoms are usually mild however and respond to 5 or 10 grain doses of acetyl salicylic acid at 3 to 4 hour intervals More severe symptoms in addition require ¼ (15 mg) or ½ grain (30 mg) doses of codeine

Relief of aggravating or exhausting cough although infrequently a part of the clinical picture may require attention and treatment The most effective suppression of cough is obtained with anodynes (For treatment of cough consult section on Chronic Bronchitis and Bronchiectasis) Since there is no specific treatment for the pulmonary phase of this syndrome the symptoms are treated as they arise Those already mentioned are the most frequent However if other symptoms appear or if complications occur they are treated according to the specific symptom or complication

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EMPYEMA

The successful treatment of pyothorax depends on the accomplishment of the following objectives sterilization and removal of the fluid and obliteration of the empyema cavity with subsequent re expansion of the lung The overwhelming majority of non tuberculous empyemas is due to the pneumococcus streptococcus and other bacteria with known susceptibility to available antibiotic agents Nonsurgical achievement of the enumerated objectives in the treatment of these empyemas depends on the intelligent utilization of indicated antibiotics systemically and locally The method of treatment is generally the same as that recommended for antibiotic susceptible serofibrinous exudates There are a few important differences in technic The fluid must be aspirated completely each day and the pleural cavity washed with normal saline solution Re expansion of the lung should not be too rapid Loculated collections of pus may develop if re expansion occurs before sterilization of the pleural cavity is accomplished Once sterility of the pleural cavity is achieved re expansion of the lung should proceed without restriction It is imperative to follow the condition of the underlying lung with daily roentgen ray or fluoroscopic examinations throughout the duration of the treatment Additionally bacteriologic studies of the fluid must be performed each day These precautions will provide important information regarding endothorax and facilitate intelligent and safe management of each case Conservative management must be abandoned however if demonstrable evidence of clinical and bacteriologic improvement is not apparent after 3 or 4 days of treatment Failures are common in mixed putrid encapsulated and loculated empyemas Likewise empyemas which develop in spite of antibiotic therapy for the primary disease are also apt to resist conservative management

Empyemas associated with bronchopleural fistulas rarely respond to this form of therapy Poor results predominate the over all clinical results achieved in the treatment of chronic

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pleural cavity is freed of infection Empyemas due to septic pulmonary infarction may also respond to conservative management only to recur each time an infected embolus lodges in the lungs Lasting cures in this instance will be achieved only after proper surgical treatment of the primary disease In the face of therapeutic failure conservative management of empyema should be abandoned The patient should be given the benefit of surgical treatment without undue delay Systemic and local administration of

antibiotic agents in indicated cases prior to surgical intervention will augment the therapeutic benefits of surgery Postoperatively, the use of systemic and local antibiotic therapy is definitely indicated and unquestionably exerts a beneficial effect on the course of the disease

It may be mentioned in passing that tuberculous empyemas rarely respond to conservative medical management For a detailed discussion of this subject the reader should consult a satisfactory textbook dealing with the treatment of tuberculosis

Supportive therapy in the conservative and surgical management of empyema is important One should pay attention to the general condition of the patient Maintenance of a satisfactory state of nutrition is an essential prerequisite to successful conservative or surgical treatment of empyema Anemia, malnutrition, and avitaminosis are quite common Anemia should be treated with repeated blood transfusions The treatment of malnutrition and avitaminosis requires a nutritious diet high in carbohydrate protein and vitamin content The diet should be supplemented with additional vitamins by mouth or parenterally Occasionally, the use of any of the popular protein preparations is indicated Other complications are treated as they arise

Successful treatment of pyothorax requires the close co operation of the internist and surgeon Both must be open to suggestion and constructive criticism If a feeling of mutual respect for each other's opinions prevails, patients with empyema will derive the full therapeutic benefits of co operative medical and surgical management of their disease

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PNEUMOTHORAX

The treatment of spontaneous pneumothorax depends entirely on its type and extent Closed pneumothoraces usually require only symptomatic care The amount of time required for the resorption of the gas depends on the size of the pneumothorax and the condition of the pleura Usually, even the larger ones disappear within one month, and with the smaller ones it is only a matter of days Indicated analgesics and sedatives of choice may be used, respectively, for the control of pain and apprehension Occasionally, the use of oxygen is warranted Aspiration of some of the pleural gas is rarely necessary Follow up exam [illegible]

spontaneous pneumothorax recurs frequently it may be advisable to establish pleural symphysis To accomplish this objective we feel that the introduction of various irritants into the pleural cavity may be of value In this connection the use of the patient's own blood, 50 per cent dextrose solution and the insufflation of various powdered substances such as ordinary talc may be tried Since the resulting aseptic pleuritis may be quite troublesome this form of therapy should be reserved for the more serious types of pneumothoraces The best treatment for the mild closed type is bed rest and symptomatic therapy

Treatment of the open type of pneumothorax is generally similar to that of the closed variety Paralysis of the hemidiaphragm on the affected side may be beneficial Tension pneumothoraces require immediate heroic therapy The use of a water trap is indicated in all these cases To obtain the maximal benefit without delay a 13 gauge needle should be used in the thorax It should be introduced only far enough to permit the escape of the gas trapped in the pleural cavity If it projects too far into the endothorax additional tears in the pleura may result from coughing or any other activity which brings visceral pleura closer to the thoracic wall The glass outlet tube should project no more than 1 cc below the level of the water in order to obtain satisfactory results When bubbling ceases, the rubber tubing may be occluded temporarily with a suitable clamp After a satisfactory period of observation, if the patient manifests no further signs or symptoms of increasing pressure in the pleural cavity the water trap may be disconnected Before removing the needle from the chest it is advisable to obtain a manometric reading of the intrapleural pressure Since tension pneumothorax represents a real medical emergency, no time should be lost in reducing the intrapleural pressure Sterile technic is desirable in accomplishing this result, but

on occasion there is no time for sterilizing the skin or for the production of a satisfactory local anesthesia The introduction of the needle into the chest without delay is the paramount objective in the event of tension pneumothorax When pneumothorax and pleural effusions coexist, therapeutic considerations are influenced chiefly by the nature of the fluid involved The management of the various types of pleural effusions is discussed in previous sections of this presentation

In cases of spontaneous pneumothorax with a tuberculous etiology and demonstrable pulmonary tuberculosis, it is advisable to continue the pneumothorax if possible

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DISEASES OF THE MEDIASTINUM

INFLAMMATION OF THE MEDIASTINUM

The treatment of acute mediastinitis depends entirely on the nature and extent of the inflammatory reaction in the mediasti- [illegible] phagitis Specific therapy for the mediastinal disease is generally unnecessary since the process will automatically subside with effective treatment of the primary disease The indicated therapeutic measures will depend entirely on the nature of the responsible primary infection Even before the era of sulfa drugs and antibiotic agents the prognosis in this condition was favorable The clinical management of nonsuppurative mediastinitis is entirely medical

Acute Suppurative Mediastinitis This is a serious condition, immediate recognition of its presence is the key to successful treatment since its course is fulminating and frequently fatal Treatment is both medical and surgical Large doses of a sulfa drug and indicated antibiotic agents are to be given Since acute suppurative mediastinitis is most frequently the result of trauma, the simultaneous administration of penicillin, streptomycin, and the sulfonamide of choice is indicated Treatment with chemotherapeutic drugs and antibiotic agents should precede surgical drainage and be continued postoperatively in large doses until the desired results are achieved In order to save a life, the treatment of acute suppurative mediastinitis should be nothing short of heroic A large number of cases follow accidental perforation of the esophagus during instrumentation The bulk of these inflammations can be prevented by observing the necessary precautions prior to, and during, instrumentation An immediate gastrostomy should be performed following esophageal perforation which results from instrumentation or from intrinsic disease of the esophagus such as carcinoma One is then confronted with the additional problem of maintaining a satisfactory state of nutrition This objective is sometimes difficult to achieve in the presence of mediastinal suppuration A well balanced, high caloric diet supplemented by large doses of vitamins is necessary

Abscesses Localized *acute* mediastinal abscesses should be treated in essentially the same manner as acute suppuration of the mediastinum They usually result from extension of infections of the neck or from perforation of the esophagus

Chronic mediastinal abscesses are generally due to tuberculosis, actinomycosis, blastomycosis, or syphilis A tuberculous abscess usually results from involvement of the mediastinal nodes The treatment of this condition is entirely medical unless complicated by draining sinuses In this event surgical exploration may be indicated Specific therapy with streptomycin or, preferably, dihydrostreptomycin, is indicated, especially in the presence of draining sinuses Treatment with this antibiotic should be both systemic and local The early results with this form of therapy are promising, but definite conclusions must await additional investigation General symptomatic and supportive measures are important in the treatment of chronic tuberculous abscess of the mediastinum Heliotherapy in the absence of pulmonary disease may be beneficial Besides the general use of supplemental vitamins, large amounts of cod liver oil should be prescribed Roentgen therapy is [illegible]

Large doses of sulfa drugs and penicillin are indicated in the *treatment of actinomycosis* Treatment is continued until the expected clinical results are achieved and maintained Surgical excision of infected tissue and sinuses may be indicated and is frequently necessary to accomplish a permanent cure

The medical management of blastomycotic mediastinal infection is hopeless Treatment is entirely symptomatic Excision of localized abscesses is the procedure of choice The use of iodides *and other medical measures* are not even worth a therapeutic trial Syphilis [illegible] Treat-

therapy

The pain due to mediastinitis will respond to the usual symptomatic measures The judicious use of narcotics is frequently necessary to alleviate the excruciating pain of localized and diffuse mediastinal inflammations

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SPONTANEOUS MEDIASTINAL EMPHYSEMA

Spontaneous mediastinal emphysema is usually a self limited process In many instances the diagnosis is overlooked because of the paucity of significant symptoms or because of the physician's low index of suspicion If the air manages to escape into the tissues of the neck, the clinical manifestations are likewise mild Symptomatic treatment will suffice in most instances The control of *pain and apprehension* is the major consideration Suitable narcotics or sedatives should be prescribed generously

Larger mediastinal accumulations of air under pressure and those cases with an associated tension pneumothorax require more active and sometimes truly heroic treatment In these instances, the clinical manifestation of pain, dyspnea, cyanosis and apprehension may reach alarming proportions Unless immediate and energetic treatment is instituted, *cardiac embarrassment shock, or a fatal out*come may supervene quickly

In the presence of an associated tension pneumothorax, effective relief of the alarming symptoms may be accomplished by establishing an avenue of escape for the air from the involved hemithorax For a detailed discussion of this procedure the reader is referred to the section on Pneumothorax In the event that the air is trapped and confined to the mediastinum an artificial route of escape must likewise be provided This is best accomplished by an adequate incision in the suprasternal notch Aspiration of air from the mediastinum by needle is not rec*ommended The associated hazards* are too numerous and the procedure requires real skill Complete bed rest is indicated until all the symptoms and signs have subsided Since mediastinal emphysema has a *tendency to* recur, drastic limitation of activity is indicated for several weeks following the original episode; In some cases relief of dyspnea may only require the use of oxygen therapy

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FUNCTIONAL RESPIRATORY DISEASE

HYPERVENTILATION SYNDROME

The syndrome of hyperventilation occurs most frequently in psychoneurotic individuals Certain organic diseases, however, may produce the same clinical picture through involuntary alteration of the normal depth and rhythmicity of respiration Occasionally, it may be the result of vigorous exercise As a rule, the syndrome does not follow ordinary physical exertion unless the *subject is in* poor condition or suffering from *fatigue The hyperventilation* syndrome identified with psychoneurotics is a self induced clinical manifestation of emotional instability Anxiety, apprehension, or general tenseness individually *or in combination,* are the responsible predisposing psychic and emotional factors The altered respiratory pattern is characterized by overbreathing either in depth or in frequency *As a result there* is an excessive loss of CO_2 which results in alkalosis The resulting symptoms of dizziness paresthesia, tachycardia tetany, and cyanosis

respond dramatically to a variety of simple therapeutic measures The beneficial effects of symptomatic treatment of hyperventilation however, are usually temporary Permanent cures can be expected only after correction of the responsible organic disease or psychoneurotic basis The nature of the underlying organic disease frequently precludes the possibility of lasting results Such is the case when hyperventilation is the result of encephalitis lethargica and tumor of the floor of the fourth ventricle

As previously indicated, lasting cures in these instances can be expected only after identification and correction of the responsible psychic factor Identification of the psychic factor demands careful and prolonged psychiatric investigation This study by the usual clinical methods commonly ends in failure Narcoanalysis is generally necessary since the primary cause is frequently submerged in the subconscious On occasion the responsible psychic factor is apparent to both physician and patient Following accurate identification of the primary cause psychotherapy commonly fails to accomplish permanent or worth while clinical benefits To date the available and tried psychotherapeutic measures including electric shock therapy, have produced generally disappointing results Painstaking attempts at education and readjustment of the patient commonly end in failure Rationalization or removal of the provocative factor are equally difficult Hyperventilation tends to recur with monotonous and discouraging regularity even after the original psychic cause is eliminated The inherent weakness in the emotional composition of these patients will provoke the abnormal response when they encounter ordinary problems of daily existence They are unquestionably constitutionally inferior The present psychotherapeutic approach to this group of patients is obviously inadequate and demands intensive study

When the symptoms of hyperventilation occur they demand immediate action Procrastination on the part of the physician and the patient's apprehension together contribute to the evolution of an alarming clinical picture Apprehension predisposes to continued overbreathing and vice versa A state of shock may supervene unless the vicious cycle is broken Inhalation of a 70 per cent oxygen and 30 per cent carbon dioxide mixture will afford prompt relief Intravenous calcium produces equally dramatic but transient results The mechanism by which calcium exerts its beneficial effects in this syndrome is not understood clearly Ammonium chloride may be used in an attempt to prolong the effects of the more rapidly acting therapeutic measures Sixty to 80 grains (4 to 5 gm) daily, in divided doses, are required Clinical results with ammonium chloride are discouraging The patient's symptoms regularly penetrate this weak symptomatic barrier after short periods of subjugation Breath holding and rebreathing of expired air also are capable of producing rapid symptomatic relief Demonstration of these palliative technics in the presence of a patient's family or friends may have added therapeutic benefits The indulgent concern of these people for the patient's welfare is a wonderful demonstration of devotion but only serves to multiply the patient's clinical symptoms Psychoneurotics enjoy pity and attention The prompt alleviation of the clinical symptoms with any of the above methods occasionally results in permanent cures With the treatment as a starting point, a simple explanation of the mechanism involved in the production of the hyperventilation syndrome is helpful Aviators and athletes who are innocent and accidental victims of this syndrome derive permanent benefits from this practice The intelligent and co operative patient will also benefit from a purposefully induced hyperventilation syndrome With these patients the results achieved from in-

ably due to overactivity of the adrenal gland The use of a sympatholytic drug such as ergotamine tartrate is indicated in this circumstance Its use should be continued as long as there appears to be increased activity of the autonomic nervous system The use

amounts may serve to break the vicious cycle and prevent the development of a permanent deep seated chain reaction All in all, the treatment of the psychoneurotic patient who suffers from the syndrome of hyperventilation is at this time wholly inadequate and the results are correspondingly exasperating

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HICCOUGH

Hiccough is due to a wide variety of causes which irritate either the afferent pathway to the centers in the upper cervical part of the spinal cord, the centers themselves, or their efferent pathway to the diaphragmatic and accessory muscles of respiration In addition to the multitude of organic diseases which may cause hiccough (*singultus*), there may be a psychogenic origin Treatment depends on the etiology Regardless of the cause persistent hiccough is commonly refractory to all forms of treatment The frequent failure to control this annoying symptom has given birth to a panorama of therapeutic recommendations perhaps second to none in the medical management of disease The primary consideration in the treatment of hiccough should be identification of the responsible disease After this objective is accomplished successful treatment of the underlying disease will automatically abort the attack Unfortunately many of the responsible diseases are not remedial and in other instances equal difficulty accompanies the effort to assign a specific cause for the development of singultus At this point the physician usually embarks on a trial and error attempt to control the attack symptomatically Simple hiccough usually requires no therapy and its spontaneous termination rivals the suddenness which marks its onset No doubt many of the recommended measures for the control of hiccough owe their birth directly to this fact The therapeutic armamentarium unquestionably contains a large inventory of recommendations which owe their recorded success to a fortuitous application which accidentally coincided with spontaneous recovery from an attack Failure to control persistent hiccough with all but a few of the recommended procedures substantiates this conclusion

Hiccough which is associated with various gastric d seases ma h ... by the ... ture of ... ministration of hydrochloric acid or gastric lavage Treatment depends on the nature of the gastric disorder When certain intestinal disorders such as acute pancreatitis typhoid fever, acute appendicitis, obstruction or ileus are the cause of an attack relief of the symptoms will result from successful treatment of these conditions A cathartic or an enema ...

use of sedatives and the judicious administration of a narcotic drug may prove beneficial Recovery frequently follows restful sleep induced by the necessary amount of intravenous sodium amytal

Rebreathing breath holding and the inhalation of a 90 per cent oxygen 10 per cent carbon dioxide mixture have a common mechanism and have proved successful in our experience The use of indicated intravenous preparations to correct the electrolyte and water balance has a definite place in the management of those cases which complicate such conditions as diabetic coma and uremia ... nd traction ... ed position ... cold water sometimes produce relief Light anesthesia is an effective measure and deserves early consideration Pressure applied to the phrenic nerve between the heads of the sternocleidomastoid muscle or application of ice bags or an ethyl chloride spray in the same area is frequently beneficial Before surgical interruption of the phrenic nerve by crushing division or avulsion is resorted to all of the more conservative medical measures should be tried Persistent hiccough however is occasionally associated with alarming symptoms which necessitate consideration of heroic measures Relief of distention in the postoperative patient will frequently control an attack There are innumerable other recommended measures for the symptomatic relief of hiccough The bulk of these recommendations is cloaked in a penetrating and stifling aroma of quackery and does not merit repetition

When hiccough is a manifestation of psy

chogenic origin, the problem is even more difficult Electric or insulin shock therapy may abort the attack Application of psychotherapeutic measures commonly fails to produce permanent or even temporary relief The discussion of the psychiatric aspects is essentially the same as that found in the [illegible] satisfactory

Quinine sulfate	grains xxiv
Tincture of valerian	dram i
Milk of asafetida	oz i
Water q s ad	oz iii

We have found that a teaspoonful of this horrible, but harmless, concoction every 4 hours, day and night, will abort an attack in most psychoneurotic individuals when other more popular measures have failed

Hiccough which results from the presence of tumor masses in the mediastinum will be controlled following surgical removal Roentgen therapy may be used for radiosensitive masses The treatment of refractory persistent hiccough requires a therapeutic trial with all of the recommended measures Relief of the patient's symptoms and the physician's exasperation may come from the least expected source Hiccough has a monotonous tendency to recur Should this happen, the use of the previously effective measure is indicated immediately This practice, however, is frequently attended by clinical failure Consequently, the tedious procedure of therapeutic trial with the multitude of recommended measures is again necessary The same treatment which relieved hiccough on one occasion will fail on subsequent occasions Conversely, previous failure with a therapeutic measure does not preclude the possibility of future success

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pressure in the systemic circuit is higher than that in the pulmonary circuit Under such circumstances some of the aerated blood is sent a second time to the lungs Cyanosis is absent If, however, there is some obstruction to the outflow of blood from the right side of the heart, blood may be shunted from the venous to the arterial side If a sufficient amount of blood is thus shunted, cyanosis results There are also a number of anomalies involving the heart or great vessels in which no shunt exists Hence Dr Abbott established the following classification

I Cases of arterial venous shunt
II Cases of venous arterial shunt
III Cases in which there is an absence of shunt

It is an interesting fact that surgery has been used successfully for cardiovascular defects in each of these three groups

Surgical Treatment PATENT DUCTUS ARTERIOSUS In 1939 Gross and Hubbard reported the first successful ligation of a patent ductus arteriosus Since the pioneer work of Gross many other surgeons have entered the field, so that at present the operation is quite well standardized and in expert hands carries a low mortality On one point the surgeons are not yet completely agreed, and that is whether the ductus should be ligated or severed The objections to ligation are that a good deal of foreign material is left in the chest and that in a small percentage of cases recanalization of the ductus occurs The objection to severing the ductus is the danger of uncontrollable hemorrhage At the Children's Memorial Hospital Dr W J Potts has, at the time of writing operated on 72 patients with patent ductus In the first 20 ligation was done The remaining 52 have all been severed Because of a special ductus clamp which he has devised, he feels that the danger of hemorrhage is practically eliminated There has been no fatality or serious complication in either group

The ductus arteriosus is normally open during fetal life It arises from the pulmonary artery near the bifurcation of the right and left branches and enters the aorta just distal to the origin of the left subclavian artery In normal cases the ductus closes within the first 2 or 3 months of life Why in certain individuals the ductus fails to close, and even becomes enormously enlarged, is not known

In uncomplicated cases of patent ductus, blood passes from the aorta to the pulmonary side Inasmuch as the shunt is arterial venous, cyanosis is absent It has been shown that in cases of patent ductus the amount of blood shunted may be as much as 70 per cent of the blood leaving the left ventricle It is obvious that under such circumstances the work of both ventricles is increased

The symptoms and signs are poor appetite, underweight, easy fatigability, cardiac enlargement a machinery murmur present at the base of the heart, and a capillary pulse The diastolic blood pressure is low In many instances the roentgen film shows

the typical physical signs of a patent ductus but *who manifest no evidence of* cardiac overwork It is a debated question whether these children should be submitted to operation There are arguments in favor of operation in these circumstances Bacterial endarteritis is less likely once the ductus has been closed The operation is safer and easier in children, hence if surgery is contemplated it should not be too long delayed It is essential that precautions be taken to eliminate the possibility of associated anomalies which might contraindicate closure of the ductus Pulmonary stenosis is an example of such a lesion Therefore, any degree of cyanosis even on exercise, appreciably decreased oxygen saturation of the arterial blood, or right heart strain in the electrocardiogram should make one wary as to the advisability of closing the ductus

The good effects of operation in the typical case are almost immediately apparent The appetite is improved, there is a gratifying gain in weight, and exercise tolerance is increased Following operation the heart is less tumultuous, the pulse pressure is normal, and the heart shows, after some months a definite decrease in size

CONGENITAL PULMONARY STENOSIS Con ... ne of the more ... t rarely ... d most frequently in conjunction with defect of the ventricular septum, dextroposition of the aorta, and hypertrophy of the right ventricle This syndrome is known as the tetralogy of

Fallot In this condition there is an inadequate supply of blood to the lungs because of the pulmonary stenosis Because the aorta overrides the ventricular septal defect some of the blood from the right ventricle is pumped directly into the aorta Hence a portion of the venous blood passes directly into the arterial circuit without traversing the

the lungs and that by the same token the pulmonary flow is so small that insufficient blood reaches the lungs for aeration Cyan

creased flow of blood to the lungs would relieve cyanosis to some extent and increase the childs exercise tolerance and general well being This was accomplished by doing an end to side anastomosis between one of the branches arising from the aortic arch (usually the subclavian artery) and the right or left pulmonary artery The results of this operation were better than they had dared to hope Children who had been extremely cyanotic markedly underweight unhappy and fretful and unable to walk more than a few steps were transformed into children whose cyanosis was greatly relieved who were able to play almost as do normal children and who showed a profound improvement in their general outlook on life In 1946 Potts Smith and Gibson reported a modification of the Blalock operation whereby a direct anastomosis was made between the aorta and the pulmonary artery This was made possible by the use of a clamp which encircled the aorta and merely pinched off a lip of the vessel thus allowing blood to course through the aorta while the anastomosis is being performed The principle of the operation varies in no way from that of the Blalock operation

Diagnosis of the tetralogy of Fallot rests upon symptoms physical examination roentgenographic and fluoroscopic examination the electrocardiogram and oxygen studies of the peripheral blood In doubtful cases cardiac catheterization and angiocardiography may be helpful in arriving at a diagnosis

There are certain general principles which should be observed in performing the Blalock or Potts Smith operation for the relief of congenital pulmonary stenosis These patients are in serious condition and therefore the surgical risk is great Inasmuch as the operative risk is greater in young infants operation should be deferred until the patient is 1 or 2 years old when the condition is sufficiently benign to permit waiting Great care must be taken to see that the patient is free from respiratory or other infection at the time of operation Penicillin should be given for 24 hours prior to operation and for several days following operation Expert anesthesia is just as important as expert surgery Inasmuch as the chest is open one lung partially collapsed and one pulmonary artery occluded during the anastomosis it goes without saying that the margin of safety is extremely small Dr William O McQuiston who has been the anesthesiologist in practically all of the "blue baby operations carried out at the Childrens Memorial Hospital has regularly employed an endotracheal tube and cyclopropane with a high percentage of oxygen has been the usual anesthetic

It can be readily understood that so extensive a surgical procedure carried out in an infant or child so seriously handicapped will carry an appreciable mortality In a series of 189 cases of congenital pulmonary stenosis operated on by Dr W J Potts and his associates the over all mortality where anastomosis was completed was 9 3 per cent The highest mortality occurred in babies under 1 year of age In fact in all patients between the ages of 3 and 16 years the mortality was only 3 8 per cent

Regardless of the poor condition of any patient operation is obligatory if one can be certain of the diagnosis Some of the patients who seemed utterly unable to stand the shock of the operation came through the procedure in splendid shape and showed truly amazing postoperative benefit

The outlook without operation is so poor that the surgical risk is well justified

Coarctation of the Aorta The adult type of coarctation of the aorta consists of a localized constriction of the aorta usually at a point just distal to the origin of the left subclavian artery

In 1945 Crafoord and Nylin reported the

first successful operation for this condition This operation consisted in excising the narrowed portion of the aorta and doing an end to end anastomosis This technically difficult operation has proved to be feasible in lowering the excessive blood pressure in the upper portion of the body and supplying a more effective circulation to the lower portion In the majority of instances patients with coarctation of the aorta are free of symptoms during childhood and have a normal exercise tolerance It has been quite clearly shown however, that the majority meet with disaster before they have lived out a normal span of life The chief causes of death are bacterial endarteritis, rupture of the aorta cerebral vascular accidents and heart failure

It would seem therefore, in cases where the hypertension in the arms is at all extreme, that the possible danger from these complications would justify the surgical risk involved At the present time it is fairly well accepted that the operation is both easier and of greater benefit in childhood The optimal time for operation is between the sixth and 15th years

Double Aortic Arch In 1945 Gross reported the first successful operation for the relief of symptoms due to a double aortic arch In this condition both the right and left fourth branchial arches persist The ascending aorta divides into two portions, the anterior portion passing in front of the trachea and esophagus, while the posterior portion passes behind them These two portions of the aorta unite to form the descending aorta It is thus seen that the trachea and esophagus are completely encircled by a vascular ring In many instances the trachea and esophagus are so compressed that serious and even fatal symptoms may result The symptoms are those which result from interference with the airway—a wheeze, a brassy cough difficult respiration and frequent respiratory infections Less often dysphagia is also present, particularly on the effort to swallow solid food The diagnosis is made by noting on roentgenographic or fluoroscopic examination a compression of the barium filled esophagus at the level of the aortic arch, and by a similar compression of the trachea as visualized by direct bronchoscopy or the use of lipiodol

The surgical procedure consists in severing one segment of the vascular ring By this means the constriction of the trachea and esophagus is relieved The operation should be performed as soon as the diagnosis is made inasmuch as the patient is in constant danger both from obstructive symptoms and respiratory infections

Medical Treatment In spite of the great contribution of recent surgery in congenital cardiovascular anomalies there are still many children with types of anomalies which, in the present state of our knowledge, cannot be relieved by surgical means

For this group of patients too often neglected, it is our obligation to plan a regimen which will give them as satisfactory a life as circumstances will permit Many of these patients suffer from so mild a form of congenital heart disease that they can enter into the usual activities of childhood Even in the more severe cases, especially those which are cyanotic, it is usually not necessary to restrict their exercise It is difficult for the parent, and sometimes for the family physician, to accept this point of view Yet it must be remembered that these children have grown up with their handicap and from their first attempts at exercise they have learned how much they are able to do Hence they will stop of their own accord when they become tired They should not be placed in gymnasium classes or in competitive games if experience has shown that they become

ould be
normal
ed out

Every effort should be made to avoid respiratory or other infections Tonsillectomy and tooth extraction should be done when indicated Because of the ever present danger of bacterial endocarditis, the sulfonamides or penicillin should be administered prior to operation and for a few days thereafter Other surgical procedures should be carried out when indicated One is constantly amazed to see how well the "blue babies" tolerate the long and strenuous surgical procedure necessary for their relief This furnishes ample evidence that the usual major operation will be well tolerated

One of the dangers to which the cyanotic child is exposed is that of cerebral thrombosis This danger is increased by dehydration.

Hence an adequate fluid intake should be scrupulously maintained especially in warm weather or in the presence of fever Upon the appearance of the first signs of cerebral thrombosis venesection and heparin are in dicated together with intravenous fluids un til the patient is able to take fluids by mouth

dose hourly as necessary to maintain the clotting time at 20 or 30 minutes

Paroxysmal dyspnea is a frequent occur rence in infants suffering from severe anox emia The infant becomes limp the breath ing is difficult the cyanosis becomes markedly increased and unconsciousness may super vene He should be immediately placed in

face down with his legs drawn up under him

Subacute bacterial endocarditis is a con stant menace to the child with a congenital cardiac defect Before the days of modern chemotherapy it was the most feared compli cation With the advent of penicillin the dangers resulting from this complication have been greatly reduced

The management of heart failure in con genital heart disease is similar to that in ac quired heart disease Complete bed rest is indicated Oxygen is helpful Digitalis should be administered in accordance with the usual rules One cat unit for each 10 lbs of the patient s weight is usually considered the average digitalizing dose if given within a 24 hour period One half the digitalizing dose may be given initially followed by the re maining half in divided doses at intervals of 6 hours In urgent cases the digitalis may be administered intramuscularly The daily maintenance dose of digitalis is estimated to be about one tenth of the amount necessary to produce digitalization It should be em phasized however that there is extreme variation in the tolerance of children to digitalis I have seen many instances where more than twice the usual dose was neces sary to produce a digitalis effect and others where the usual dose quickly induced digi talis intoxication

In the infant or young child vomiting is the chief symptom of overdosage of digitalis

Careful and frequent auscultation of the heart is essential to detect disturbances of rhythm Frequent electrocardiograms may serve to show the approach of digitalis in toxication before other symptoms or signs are manifest

genital heart disease The fact that he has a relatively incapacitating lesion does not nec essarily condemn him to an early death or a useless unhappy life The famous musician with tetralogy of Fallot who lived to the age of 60 years should convince us that we have not only the right but the obligation to as sume a hopeful attitude in our management of these patients Occupations should be planned which lie within their physical pos sibilities They must be encouraged to seek a responsible satisfying life rather than using their physical handicap as an excuse for lead ing an aimless existence

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THE CARDIAC ARRHYTHMIAS

In considering the treatment of any cardiac arrhythmia it must always be kept in mind that the abnormal rhythm is not a disease of itself It is a symptom either of definite car diac damage or of some extrinsic factor which influences the heart mechanism This

must not be forgotten no matter how successful the treatment of the arrhythmia may be This sounds like an unnecessary commonplace, *but it is frequently forgotten*, especially when the rhythm remains normal after a lapse of time

Paroxysmal Auricular Tachycardia Paroxysmal auricular tachycardia is one of the least serious of the cardiac arrhythmias, so far as health or life is concerned But it is one of the most troublesome and inconveniencing problems for the patient, and troublesome to the physician because he has at his hand no one specific remedy which might be uniformly helpful

The immediate attack of paroxysmal tachycardia does not require any treatment of itself when it is of short duration and when it produces no uncomfortable symptoms Attacks which last long enough to cause uncomfortable symptoms or which are frequently repeated will demand attention

In the case of attacks of shorter duration, the patient may continue with what he is doing, and the symptoms may disappear, or he may stop and stand erect Usually, however, the attack will stop more promptly if the patient sits down until it is over, or, when possible, assumes a recumbent position

There is an infinite variety of simple methods for stopping *an attack, such as sitting in* a chair and bending forward, with the head between the knees, or taking a deep breath and holding it It may be stopped by taking a deep breath and coughing, or inhaling with glottis closed or by lying down with the feet higher than the head or by lying on the back with the arms outstretched and breathing *deeply* Forcing a belch may stop the attack Putting the finger in the mouth and initiating a gag reflex or even emesis may be benefici[illegible]

or [illegible]

methods recourse may be had to carotid sinus stimulation This is effective in most cases The carotid sinus is located by the fingers at the level of the carotid artery and the thyroid cartilage It is better to use all four fingers in order to cover a wider area and be sure of finding the sinus Pressure should be firm over the artery, compressing it *between the* palpating finger and the vertebral column for a few seconds, changing *the position of the fingers if there* is no response A massaging motion may be used Which side is stimulated makes little difference and usually the response is prompt Both sides should not be stimulated simultaneously Stimulation may be accomplished more readily by standing behind the patient when he is in a sitting position However in some cases, it *may be more effective when* the patient is prone in bed The response can usually be felt by the palpating finger *Unless the attack has lasted* long enough to cause evidence of cardiac decompensation the patient is usually aware of the change in rhythm at once It is a simple procedure, and there are many instances in which someone in the family may be instructed in its use Some patients can do it themselves

Pressure upon the eyeball may cause a *similar reflex It is unpleasant to some* patients and usually not as effective as other methods Nevertheless, there are a few instances where it is effective when carotid sinus pressure is not

Syrup of ipecac is often effective in stopping the paroxysms It is given in doses of 1 to 2 drams (4 to 8 cc) repeated in one hour, if necessary Emesis may result, and if so the medication may be more effective

Quinidine sulfate may be used orally in *attacks resistant to other treatment* It can be given in 3 grain (0 2 gm) capsules every 2 hours for six to eight doses If there is an idiosyncrasy, it should reveal itself in the first one or two doses, and the drug is to be stopped if there is any evidence of quinine poisoning, such as tinnitus, dizziness, nausea vomiting diarrhea, or urticaria It may be continued for several days Quinidine may be used parenterally if necessary Not more than 7½ grains (0 5 gm) should be given *slowly by the* intravenous route, and administration is to be stopped at once when the normal mechanism returns It can also *be given intramuscularly*, 7½ grains (0 5 gm.) every 2 hours, up to three to five doses if necessary Dihydrochloride quinine, 0 3 gm. may be used if quinidine *is not available*

Acetyl beta methylcholine may be used if it is administered carefully, and may be adequate when other means fail *It should be* remembered that the sun shines equally on the just and the unjust, and evidence of vagal stimulation may occur elsewhere, which may

be not only undesirable but definitely alarming Doses of 1/6 to 2/3 grain (10 to 40 mg) may be used intramuscularly, with a constrictor applied proximally, released at intervals, allowing a gradual absorption or a rapid termination of absorption should symptoms appear A syringe loaded with atropine, 1/100 grain (0 6 mg) should be immediately available The propriety of the use of acetyl beta methylcholine is doubtful

Neostigmine, 1/150 grain (0 4 mg) intramuscularly, has been used successfully to abort the attacks, or prostigmine bromide, 15 mg , may be used by mouth two or three times a day to prevent the attacks

Sedatives, such as bromides or one of the more rapid acting barbiturates, i e , 0 1 gm of seconal, are always of some use, and may aid a great deal in the efficacy of the more simple measures Morphine sulfate 1/4 grain (15 mg) is sometimes of value, especially if it tends to bring on nausea, but the danger of its being habit forming if used repeatedly should be kept in mind Carotid sinus pressure may be more effectual after a sedative

Potassium and/or magnesium salts are best reserved for hospital practice

In every case of paroxysmal tachycardia, as in all of the arrhythmias, every effort should be made to determine what is the underlying cause or what is the trigger mechanism Our efforts are often fruitless but are not as hopeless as is usually assumed

There are probably more cases of paroxysmal tachycardia which are migraine equivalents than are recognized, and a careful personal family history should be taken

cases are migraine equivalents In some instances desensitization is successful Allergy may be a factor, even though there is not a

lent prescription consisting of tincture of belladonna in elixir of phenobarbital, may be effective

Tr belladonna	8 0
Elixir of phenobarbital q s ad	30 0

Sig —1 teaspoonful 3 times daily before meals

An accompanying spastic constipation should be treated without cathartics Strychnine may be of value An achlorhydria must be considered Every possible factor should be unearthed such as the influence of fatigue, overwork, tobacco, liquor, etc Occasionally an attack will follow sudden exertion

In the instance of repeated attacks quinidine, 3 grains (0 2 gm) taken three or four times a day, may be used There are some cases in which the heart is not normal and in which there is some residuum of rheumatic carditis In some of these digitalis is of advantage, as it is in some other cases It should be used in small, carefully observed doses Occasionally its use will induce auricular fibrillation In this event it should be discontinued at once and the rhythm will return to normal However there are instances of frequently repeated paroxysms of tachycardia in which an auricular fibrillation may render management easier The auricular fibrillation can always be controlled by digitalis

Paroxysmal Ventricular Tachycardia Paroxysmal ventricular tachycardia must always be carefully differentiated from other tachycardias It should never be treated simply as a tachycardia With only rare exceptions it is of grave import, and ventricular fibrillation and death are only one step removed Treatment should be directed to the underlying cardiac disorder, of which the tachycardia is but one expression

The most frequent cause is myocardial infarction which must be treated promptly as such Coronary occlusion should be suspected in every case of paroxysmal ventricular tachycardia There will be some cases consequent upon coronary insufficiency, without actual occlusion or infarct, in which there will be short episodes of paroxysmal ventricular tachycardia which appear after effort or emotion, or apparently spontaneously Such cases may be treated with coronary vasodilator drugs, as aminophylline, 7½

bin determinations can be made

Overdosage with digitalis is a frequent cause of ventricular tachycardia In such cases the digitalis should be stopped at once If edema is present, diuretics should not be

used as *the return of digitalis laden edema* fluid into the circulation may bring on a fatal digitalis intoxication

The question as to the use of quinidine is not as simple as it sounds It does depress the irritability of the ventricular muscle but at the same time it depresses every other *function of heart muscle Its use may be of* benefit in some cases and in others it is harmful If a case of coronary occlusion is *promptly and adequately cared for there* will be little indication for the use of quinidine Sporadic cases of ventricular tachycardia are best treated by means of coronary *vasodilator drugs such as aminophylline* 7½ grains (0 5 gm) intramuscularly

If quinidine is used care must be taken not to produce any untoward reaction It is best to give 3 grains (0 2 gm) every 2 to 3 hours If any toxic symptoms appear such as nausea diarrhea or tinnitus the drug *should be stopped*

In the absence of any signs of idiosyncrasy or toxicity the drug may be continued every 2 hours night and day and if necessary the dose may be increased to 6 grains (0 4 gm) every 2 hours until the tachycardia disappears

There are doubtless occasional cases of paroxysmal ventricular tachycardia which occur without any apparent underlying pathology It is best to assume that there is some cause which has escaped attention and diagnosis

Auricular Fibrillation Auricular fibrillation almost invariably presupposes some degree of cardiac damage There are some cases however associated with a toxic thyroid in which the heart returns spontaneously to a *normal mechanism after a normal* metabolic rate is restored In some of these cases the amount of permanent cardiac damage may be slight

There are cases of paroxysmal fibrillation in which the heart is apparently normal Some of these are consequent on some extra*cardiac stimulus*, as a hiatus hernia or cholelithiasis An occasional case of fibrillation may occur as an allergic response Digitalis may induce fibrillation in some hearts in which there was previously a *normal mechanism* In some of these patients it is a question whether or not there is some degree of predisposing cardiac damage

Attacks of paroxysmal fibrillation are best treated with rest and mild sedatives such as phenobarbital ½ grain (30 mg) three times daily If a provocative condition is found, it should be cared for Digitalis is not indicated if the attack is purely paroxysmal as it may serve to perpetuate the condition If the paroxysmal attack persists quinidine may be used in a dose of 3 grains (0 2 gm) every 2 to 3 hours

Auricular fibrillation in which the heart rate is normal and in which there is no dyspnea or other evidence of passive congestion does not demand treatment It is *the rapid rate and not the fibrillation which* constitutes the mechanical disadvantage

Auricular fibrillation which has become permanent and in which the rate is rapid, always demands treatment If dyspnea and passive congestion are not already present, they soon will be if the rapid rate is not *adequately controlled For treatment*, digitalis carefully administered and carefully watched is an almost ideal drug There are few therapeutic measures in medical practice which are as efficient or as satisfactory

During the first few days or until there is little or no evidence of passive congestion bed rest should usually be enforced The degree and extent of the bed rest will, of course depend primarily on the cardiac condition

The dosage and the rate of *administration* should be guided by observation of the clinical results only and not by any rule or formula although these may be useful if not taken too literally There is rarely need for precipitate haste The patient s interests will usually be adequately served if the powdered *leaf is administered in doses* of 3 grains (0.2 gm) or 1½ grains (0 1 gm) of the standard U S P pills every 4 hours or four times daily until there is clinical evidence of adequate dosage as evidenced by *decrease in pulse* rate decrease of dyspnea and cyanosis and increase in urinary output No attempt should be made to follow any rule as to pulse rate or pulse deficit The full dosage *should not* necessarily be kept up until all evidence of passive congestion has disappeared The re*sidual edema must* necessarily disappear with the increased cardiac output and increased blood flow through the kidneys If it does not other factors must be investi

gated, as kidney function, salt intake, plasma proteins, etc

Once the optimal clinical level of digitalis has been reached, a daily dosage just sufficient to maintain this level should be given For this there is also no rule, and there are wide variations in the amount of digitalis

much The effect of the dosage should be watched, and carefully adjusted as necessary Often a dose every second day is sufficient, but even this may be too much and may be toxic Whatever may be the advantage of digitalis glycosides, a constant, adequate level is more readily maintained with the more slowly absorbed and more slowly ex creted, whole leaf preparation

Patients may be maintained for years in a satisfactory state of health as far as the fibrillation itself is concerned Untoward changes may occur because of intrinsic cardiac conditions, and they occur frequently

dosage often closely approximate one another Hope observed in 1834 that digitalis increases blood coagulability Intravascular thromboses may be induced (de Takats, Trump, and Gilbert) Digitalis also acts as a coronary vasoconstrictor in the higher levels of dosage, and often in levels not so high (Gilbert and Fenn) Because of this, it has the additional disadvantage of inducing degenerative changes in the heart muscle (Kyser, Ginsberg and Gilbert) These changes can be obviated in large part by the daily administration of coronary vasodilator drugs such as aminophylline or theobromine calcium salicylate (theocalcin) Quite apart from obviating the effects of

also taken, 1 tablet after each meal

Each patient should be taught the use of digitalis, just as diabetics are taught the use of insulin They must learn the danger signals, such as coupled pulse They should be taught to keep the pulse rate at its optimal level, and to vary the digitalis dosage accordingly They soon learn to keep the dos

can learn to take the apical pulse rate No matter how well this is done, the patient should be checked by the physician at regular intervals, this should include observation

tion of action and as to potency, they have the great advantage of more rapid absorption, and are adapted to parenteral use The physician who elects to use them should limit himself to one preparation with whose clinical use he is perfectly familiar

Digitoxin is perhaps the most useful of

had some form of digitalis In addition to this, there are wide individual variations Parenteral administration is useful in cases where a high degree of passive congestion has resulted in nausea

Quinidine is of limited value Its use should be reserved for those cases of fibrillation that show little or no evidence of cardiac damage In cases of auricular fibrillation with a toxic thyroid, it is frequently of great value after the metabolic rate has returned to normal In prescribing quinidine a test dose of 3 grains (0 2 gm) three times daily should be tried If no signs of toxicity, such as nausea, diarrhea or ringing in the ears, occur the dose may be increased to 0 2 gm every 2 to 4 hours until normal rhythm is established

In cases of actual cardiac damage, even if a normal mechanism has been restored by quinidine, the duration of the quinidine effect will usually be brief, and the clinical course no better, if as good, as it will be with digitalis Quinidine should never be

used if there is the slightest chance of an embolism being released when a normal mechanism is restored and the auricles again function normally

Auricular Flutter. While *auricular flutter* has some of the aspects of a paroxysmal tachycardia, accompanied by some degree of heart block, it is quite different in character *It is almost* invariably associated with some type of cardiac disease, as rheumatic carditis, coronary artery disease, or cardiac syphilis, or may be seen as one of the consequences of thyrotoxicosis or hypertension Rarely is it an early symptom of coronary occlusion It may occur in an apparently normal heart

Treatment of the short paroxysmal attacks should be directed toward the primary cardiac condition as well as any known precipitating factors such as fatigue, overexertion, nervous factors, or indiscretions in food or drink In attacks of short duration no treatment of the immediate attack may be necessary Occasionally a paroxysm may yield to carotid sinus pressure

When the abnormal rhythm persists it will almost invariably respond favorably to digitalis therapy, either in one way or another The powdered leaf in 3 grain dosage (0 2 gm), or the standard U S P pills, 1½ grain (0 1 gm), may be given three or four times a day until some evidences of digitalis effect occurs The rhythm may change to an auricular fibrillation If digitalis administration is discontinued at this point, the rhythm may revert to normal and no further treatment may be necessary, aside from rest and possibly small doses of quinidine for a few days In cases in which there is any reason to suspect an active intracardiac process with mural thrombi the possibility of embolism must always be kept in mind with a return to normal rhythm

If auricular fibrillation persists, digitalis should be continued in doses sufficient to maintain an optimal pulse rate If the auricular flutter persists but with a higher degree of block, maintenance dosage of digitalis should also be continued to keep the heart rate at an approximate normal

In some cases, in which a high degree of passive congestion is inducing serious symptoms, it may be advisable to secure a more prompt digitalis effect by means of one of *the more rapidly* absorbed and more rapidly acting digitalis glycosides, either orally or parenterally

If a normal mechanism is not restored by digitalis quinidine may be tried, as in auricular fibrillation It may sometimes be successful when digitalis has failed When a normal rhythm has been restored by either method it is usually best to administer small doses of quinidine, 3 grains (0 2 gm), three or four times daily, for a few days

[illegible]

treatment of the arrhythmia itself is indicated This does not mean that the condition should be blandly ignored Every effort should be made to assure the patient that the condition is not serious

A careful history should be taken to determine the possibility of any etiologic factor which could be corrected Fatigue predisposes to attacks as do emotional disturbances and excessive smoking Gastro intestinal factors such as indigestible meals or meals eaten too hurriedly may produce extra [illegible]

sponsible for premature ventricular contractions when the dosage has passed a certain point

If medication must be given because of the patient's reaction to the occurrence of these ectopic beats in spite of reassurance quinidine sulfate, 3 grains (0 2 gm) three times a day may be used Effervescent triple bromides 15 grains (1 0 gm), two or three times a day may be effective A small dose of phenobarbital ½ grain (30 mg) night and morning may help Or strychnine sulfate, 100 grains three times a day, after meals is helpful If potassium salts are used, the possibilities of harmful effects must be considered

Heart Block Heart block, either partial [illegible]

the heart block is based on intrinsic anatomic changes, these are usually of an irreversible nature, as when the block follows invasion of the conducting pathways by inflammatory processes or when it is consequent upon a congenital defect When it

is due to coronary changes, improvement may follow the use of the coronary vasodilator drug, if the fibrosis has not progressed too far Diphtheria rarely causes a permanent heart block Syphilis may cause heart block which may yield to careful antiluetic treatment Cardiac contusions, as steering wheel accidents, may cause heart block Any case of cardiac contusion should have an electrocardiogram taken at once If there are changes the patient should be kept in bed for from 4 to 6 weeks Fatal results of cardiac [illegible]

[illegible] the course of rheumatic fever or diphtheria, or some other acute infection as in cases diagnosed as influenza The block will usually disappear with the subsidence of the acute infection Temporary heart block may result from digitalis or, more rarely, from quinidine Intensive roentgen therapy directed over the heart may cause a heart block which may or may not disappear with time

Vagus stimulation from any one of several extrinsic sources may also cause heart block This may occur in cases of esophageal diverticula hiatus hernia cholelithiasis, or pleural scars from roentgen therapy Allergy to certain foods may cause a temporary heart block Pulmonary embolism may be the etiologic factor (Kauffmann), most of these cases may be obviated by attention to the causative factor

Patients showing passive congestion and in whom there is heart block may be helped by digitalis in small doses Careful observation and great care must be exercised so that the condition will not be made worse, or a complete block induced, with possibly a Stokes Adams syndrome When complete heart block is associated with Stokes Adams syndrome, watchful care and treatment are imperative keeping the patient in an environment where a sudden attack would not bring serious results Care must also be exercised in regard to the patient's activities Overexertion or fatigue may predispose to attacks Sources of vagus stimulation should be investigated One case following vagus stimulation, which resulted from pleural scars due to roentgen therapy, was free from attacks with daily doses of belladonna and phenobarbital Except in these rather unusual cases resulting from vagus stimulation, atropine is not useful

Constant daily use of a coronary vasodilator drug such as aminophylline or theocalcin over long periods of time is rational and may serve to maintain the pulse rate at higher levels and obviate the syncopal attacks When the attacks occur at short intervals, epinephrine solution 1 10 000, in doses [illegible] be used [illegible] the pulse [illegible] because it is more slowly absorbed and when the effect begins to wear off it may be renewed by massaging the site of the injection Only two or three injections every 24 hours may be needed When needs are less urgent ephedrine sulfate may be used, in doses of ⅛ grain (8 mg) to ½ grain (30 mg) as needed As small a dose as possible should be used because of its unpleasant effect in increasing nervousness Barium chloride has been used but it is not especially effective and is of doubtful propriety For emergency treatment during an attack in which death seems imminent intracardiac injections of epinephrine solution, 0 25 to 1 cc, may be lifesaving and may help after apparent death Occasionally patients may live for years after such an episode

NEWELL C GILBERT

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NEUROCIRCULATORY ASTHENIA OR EFFORT SYNDROME

Since Sir Thomas Lewis first described neurocirculatory asthenia, or as he more aptly termed it, the "effort syndrome" the basic

structure has been considerably altered A great deal has been written lately, indicating that this is a psychiatric problem In this section, however, the subject will be treated as it *concerns the practitioner of* internal medicine

It will help greatly in our therapy of this condition if we turn to Sir Thomas Lewis' original concept of a group of symptoms consequent on effort The effort syndrome is not a disease and its diagnosis requires that the heart and circulatory system be anatomically normal Neither is it a psychiatric entity, in spite of many suggestive symptoms The symptoms and physical signs are those which would appear in any of us on exertion, but in this condition they appear with a minimum of exertion and are greatly exaggerated There is a lowered threshold to autonomic stimuli and of overresponse to those stimuli Some of us might exhibit not only the same physical symptoms, but the same psychologic symptoms *as well with sufficient physical or nervous* trauma The increased incidence of this syndrome in war times is due to the fact that there is an increase in physical and nervous trauma

Our therapy will be clarified if we divide our patients exhibiting symptoms of the effort syndrome into five groups, much as Sir Thomas did with some minor and inconsequential changes

(1) A group of individuals so constitutionally *inferior that they will show symptoms* under minor circumstances, they are basically below the normal standards of physical and nervous health

(2) A group of persons essentially within normal limits of health but in whom symptoms appear after some physical trauma as gross overexertion or chronic fatigue and overwork, and who have not had sufficient rest and relaxation Such cases are frequent in daily practice The physician may observe minor *symptoms in himself* during a period of undue strain with insufficient rest This will include not only the rapid pulse, increased tendency to perspiration, and other minor symptoms, but also the lack of initiative and concentrating ability These symptoms will appear more readily in those who are less well endowed constitutionally Sufficient physical and psychic trauma will induce symptoms *in the normal person*

(3) A group of patients who were well until the advent of some infection, or even a minor operation, followed by too short a period of convalescence

(4) A group in which there is actually present some mild, silent, undiagnosed infection, such as an unrecognized tuberculosis, infected nasal sinuses, amebiasis, or any one of a group of undiagnosed *infections A mild* hypoglycemia may predispose

(5) *A group in which the trauma is largely* psychic, and in which there are doubts and fears which would be of small moment in those better endowed physically

Care of the effort syndrome is the responsibility of the physician to whom the patient goes for help and advice It should not be referred to the cardiologist or the psychiatrist Nothing should be said or done to intimate to the patient that he or she is a cardiac or psychiatric problem, one of the *great handicaps in treatment is that often* the patient has already been told by some other physician that such is the case

Each patient is an individual problem and cannot be managed by any set formula Treatment does not require any special knowledge or armamentarium What is required is common sense and a sympathetic understanding together with patience, firmness, and time The physician should start

There will be some patients in the first category *for whom he can do little,* but *whom he still can help There will be some* in the last category for whom he may need some help from the psychiatrist *But most* of them he can help greatly and restore to a comfortable and useful life

will tell the physician a great deal about the underlying conditions and what proportion of the symptoms are due to purely physical conditions and what proportion are due to an element of neurosis

A careful, detailed physical examination will do much in the way of reassuring the

patient It will help to discover what pre viously undiagnosed mild or silent infection is present If present such infection should receive appropriate treatment but there should not be any witch hunt for so-called foci of infection unnecessary care of which will only add to the physical and mental trauma This is not to be construed to mean that actual sources of proved infection should not be cared for

Laboratory examination should be com plete and may be fruitful A mild hypogly cemia may be discovered The fasting blood sugar should be determined it may be nor mal or too low values may be found after exertion or periods of nervous tension These may be improved by an appropriate high protein diet such as the Wilder diet

Treatment should be initiated by quiet friendly talks with the patient in which he is told exactly what the condition is and most important what it is not Such a talk should carry assurance of improvement but the patient must also be told that the im provement will be gradual and will depend greatly on his co operation He must under stand that relief cannot depend on a few pills vitamins hormones or vaccines And he must not be told that his symptoms are imaginary for he knows better Some of the patients certainly as many as possible should be encouraged to continue their occu pation with only the necessary modifications in their way of life and treatment should be simple so as not to attract the attention of the patient to symptoms of which he is al ready too aware

Many patients will require more rest and more hours of sleep than they are getting Sedatives should be avoided as far as is pos sible but a small dose of phenobarbital ½ ...

adjust much better with rest before and after eating It may be better to have smaller meals with something additional between them Meals should be taken leisurely sit ting quietly at a table not on a drugstore stool Med cation directed to the heart or cardiac symptoms should not be given Sup plemental vitamins may be advisable and often are necessary Tobacco and liquor are best omitted A mild carefully observed test exercise will reassure the patient and let him know that his heart is really not so bad An electrocardiogram may also be of reassurance to him

A program of physical exercise relaxation and entertainment should be worked out Both exercise and recreation should be supervised and should be increased by only small increments Overwork and overplay will only set the patient back

Many of these patients will best be cared ...

out in a rest camp provided with special facilities for rest physical therapy occupa tional therapy and recreation It is unfortu nate that there are not more co operating agencies offering such supervised care where the patient will not have to associate with nervous invalids It is also unfortunate that city hosp tals do not more frequently have associated country convalescent homes which are part of the parent hospital to which pa t ents such as these could be sent to continue under the care of the physician in the parent hospital

Under a regimen of graduated exercise ...

Bertrand Smith and others

NEWELL C GILBERT

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CORONARY INSUFFICIENCY WITH ANGINA PECTORIS

Coronary insufficiency may be said to exist at any given time when the requirement of the myocardium for oxygenated blood exceeds the flow of blood to the myocardium of the heart This situation may result from a single or a combination of a number of factors Atherosclerosis of the coronary arteries is by far the most important lesion responsible for the production of coronary arterial insufficiency and our discussion in this chapter will be limited to the treatment of this condition This pathologic process however may be present without the production of symptoms unless excessive demands are made on the heart by the superimposition of such conditions as excessive exertion severe anemia sudden hypertension tachycardia or hyperthyroid

tated by reflex constriction of the coronary arterial tree (Blumgart) The recent injection studies of the coronary arteries in cases of coronary disease have served greatly to aid our understanding of the changing pathologic process in the coronary vascular bed in these cases (Blumgart Schlesinger and Davis) The ability to develop collateral channels as a consequence of progressive coronary obstruction seems inherent in nature s scheme of preserving adequate myocardial nutrition

The characteristic pain syndrome associated with transient brief insufficiency of the coronary arteries is called *angina pectoris* When typical angina pectoris occurs without predisposing exertion the descriptive term *angina decubitus* is applicable Prolonged attacks of anginal pain associated with greater systemic reaction but without evidence of myocardial infarction are properly designated as "acute coronary insufficiency" or "coronary failure" (Master) These episodes and also the occurrence of increasing severity and frequency of the anginal syndrome must be viewed with alarm as possibly indicating progressive coronary disease or impending myocardial infarction (Boyer Waltzkin)

Prevention *Atherosclerosis* of the coronary arteries may be said to be a universal disease since it is an accompaniment of aging Coronary sclerosis is unfavorably influenced by simultaneously occurring obesity diabetes and probably hyperlipemia In recent years it has been suggested that a diet low in cholesterol content and the use of decholesterinization agents such as potassium iodide lipocaic and choline might inhibit atherosclerosis (Hermann) These measures however have not as yet proved to be of significant benefit Since a gap exists in our ability to prevent coronary atherosclerosis we can best meet the problem for those patients who are of middle age by reducing the work of the myocardium The avoidance of obesity is particularly to be emphasized The middle-aged man or woman should no longer partake of vigorous physical exertion to the extent that dyspnea and vigorous palpitation are produced Similarly emotional moderation would seem of benefit The patient in middle life who comes to his physician for advice should be impressed with the need for gradually reducing his responsibilities which lead to nervous tension He should be advised to develop interests and hobbies which require less physical effort to replace the vigorous games and sports of his adolescence and young adult life

General Measures of Treatment The physician s approach to the patient with coronary disease is of extreme importance His consultation requires unusual tact in order to support the patient s morale and yet to stress firmly the importance of a careful regimen The patient will benefit by a frank discussion apprising him that narrowing of the lumina of coronary arteries occurs in all persons as an accompaniment of age He usually eagerly grasps with new hope a statement concerning the development of collateral circulation to assist the narrowed coronary arteries in nourishing the myocardium A discussion in which instances of patients who have survived for many years of useful life are cited can be used to reassure the anxious patient to whom coronary disease often forebodes sudden death

When symptoms of coronary insufficiency

are associated with specific etiologic factors other than coronary atherosclerosis such as anemia hyperthyroidism and syphilis these influences should be eliminated with suitable therapy

The patient with coronary insufficiency will be well aware of the predisposing situations which caused his distress With these historical data it is the duty of the physician to attempt to lay out a specific program rather than merely to tell the patient to "take it easy" The patient with angina pectoris is too often dismissed with these words As a result he may be completely confused concerning what he can or cannot do This confusion helps cardiac neuroses to develop in persons who fear that every physical effort may provoke disaster To the intelligent person it is often sufficient to offer the advice that he live in such a way that he stays within the tolerance of dyspnea and anginal distress Most persons who have coronary insufficiency however will profit by more precise information Specifically telling the patient that such things as shoveling snow pushing a lawn mower or carrying a basket of clothes upstairs are hazardous will usually induce him to ask pertinent questions peculiar to his occupation which can then be discussed This approach leads to a feeling of confidence in his physician which is of immeasurable value The influence of cold air should be mentioned specifically as a precipitating factor of angina pectoris along with the comment that a scarf over the mouth and nose will largely avert attacks produced in this way Increased cardiac work and angina pectoris may be induced in persons with coronary insufficiency by emotional upsets such as outbursts of temper and by witnessing exciting athletic contests Moderation in emotional output together with avoidance of situations which induce excitement is the obvious advice needed The avoidance of physical exertion after eating should be emphasized

The physician who would treat coronary disease must not neglect the patient s other complaints and defects since they may have a profound influence on the course of the heart disease There can be little doubt that symptomatic disease of the gallbladder diaphragmatic hiatal hernia and peptic ulcers of the stomach and duodenum will aggravate the symptoms of existing coronary insufficiency Appropriate medical measures usually will counteract the influence of these conditions Hypertrophy of the prostate with symptoms of obstruction which disturb the patient s needed rest may intensify the patient s cardiac disability and justify resection of the prostate Chronic constipation and other manifestations of the irritable bowel syndrome are best treated with antispasmodics and gentle laxatives This will prevent abdominal distention with associated anginal seizures

Frequently the patient who has coronary disease is obese and this obesity offers both the physician and the patient a tangible problem to attack. The obese patient should be reduced by dietary restrictions to the average normal weight for his age and height Gradual reduction in weight on a diet which provides 1000 to 1500 calories daily is better under these circumstances than is a rigid reduction regimen

Patients with coronary disease fall prey to surgical diseases in about the same proportion as members of the general population Unfortunately the presence of symptomatic coronary atherosclerosis increases the possibility of myocardial infarction at the time of operation or in the postoperative period It is a good policy to advise the patient with angina pectoris against elective surgery of any type unless the lesion is potentially more serious than the cardiac disease or unless continuation of the surgical condition has a definite adverse effect on the heart The presence of coronary disease of course should not contraindicate surgery which is necessary for the continuation of life While the risk of operation will be increased that risk is justified for the removal of malignant tumors and for correction of such situations which result in frequent and severe colicky pain and febrile reactions usually warrant surgical intervention because such attacks if repeated will be as detrimental as the trauma of surgery

When surgery procedures are undertaken careful choice of anesthesia is indicated The anesthetic agent used should
oxygen saturation in the resp

duration of the operation and the period of general anesthesia should be the least pos sible time The blood pressure should be watched carefully in the operative and post operative period to prevent its falling to low levels since low blood pressure may be ac companied by myocardial ischemia Admin istration of oxygen by mask or tent is usually advisable during the immediate postopera tive period Unless specific contraindications are present anticoagulant therapy with di cumarol during the postoperative period can be recommended for these patients on the justifiable assumption that the incidence of postoperative coronary thrombosis and thrombo embolic complications will be less ened

Specific Measures of Treatment Rest In the past years prescription of rest for patients with coronary disease without ques tion has been much abused and has lacked intelligent application The necessity of less ening the demands on the heart by adequate rest is of course obvious but the manner in which this is prescribed must be entirely dependent on the individual needs of the patient In general the physician may justi fiably recommend for the usual patient who has exertional anginal syndrome 9 hours of rest in bed each night and in addition a period of 1½ hours of complete relaxation during the afternoon He should be advised to obtain a period of 30 to 60 minutes of complete relaxation on a couch or in a lounge chair following each meal since at those times the heart is called on for in creased work in relation to the digestion of food If anginal attacks of increased severity duration and frequency occur on less exer tion a period of *rest in bed for several days* should be advised Such progression of symp toms frequently is indicative of a progressive occlusive process with myocardial ischemia Adequate rest and the use of suitable seda tive
the
zone
larization to develop

Tobacco It has been demonstrated quite conclusively that tobacco produces vasocon striction in the arteries of the extremities (Roth McDonald and Sheard) A similar action on the coronary arteries has been reasonably well substantiated by the demon stration of electrocardiographic changes of ischemia produced in susceptible patients through smoking (Bryant and Wood) Some patients with coronary insufficiency have ob served that attacks of the anginal syndrome have been induced by smoking It also has been demonstrated that smoking tobacco in creases the carbon monoxide content of the blood and thus impairs the oxygen carrying capacity of the blood (Falk) *On the basis* of this direct and circumstantial evidence smoking should be discouraged for the pa tient with angina pectoris The patient will accept the ban more gracefully and will co operate better if he is apprised of the rea sons listed for discontinuance of the use of tobacco It is perhaps unwise for the phy sician to be too rigid in his demands of the patient with regard to the use of tobacco There are patients for whom withdrawal of tobacco induces marked irritability and emotional tension and decreases co operation for more important restrictions For such *individuals it is no doubt better* judgment to encourage moderation in use of tobacco rather than complete withdrawal

Alcohol When the physician has forbid den his patient with coronary disease the continuation of many of his previous pleas

discovered by the patient as a means of obtaining relief from his chest pain even before he consults his physician Clinically there is little doubt that 1 or 2 oz (30 or 60 cc) of whisky frequently will relieve the pain of coronary insufficiency probably be cause of its vasodilating as well as its an esthetic effect *If the patient is accustomed* to the moderate use of alcohol and he finds that it is of aid in securing needed relaxa tion he may be advised to continue to use 1 to 2 oz two or three times daily He must be warned that alcohol in excess may be of serious consequence by virtue of its action in depriving him of his ability to maintain proper restraint In some individuals use of alcohol may be a factor in in tiating abnor mal cardiac rhythms and is to be avoided Occasionally alcohol in the suggested doses will be of *considerable value in preventing* frequent attacks of angina decubitus

Diet Instruction on diet for the patient

with angina pectoris should be designed primarily to prevent obesity and to cause him to avoid large meals which make excessive demands on the heart. The patient should take three or four small meals a day. Highly seasoned, fatty, and gas forming foods should be taken in small quantities or not at all. Meals should be eaten slowly. Restriction of salt is not indicated in the diets of patients with coronary disease unless there is associated congestive heart failure which would profit by such restriction. A tendency toward constipation with associated abdominal distention and straining at the stool requires good bowel habits, the intake of sufficient fluid, and sometimes the use of mild laxatives such as mineral oil or milk of magnesia in doses of 1 to 2 tablespoons (4 to 8 cc). Considerable evidence indicates that individuals with known hyperlipemia may develop coronary atherosclerosis at an unduly early age and that the incidence of hyperlipemia is greater in patients with disease of the coronary arteries (Steiner and Domanski). Although a diet low in animal fat may not always lower the level of blood lipoids in these cases, foods rich in animal fat should be restricted.

DRUGS. Specific medicaments for use in the treatment of coronary heart disease are as follows.

Barbiturates. Nervous tension, which causes an elevation of the blood pressure, tachycardia, and probably also vasomotor coro- [illegible] r of [illegible] pro- [illegible] on [illegible]

seems to be best tolerated although continued use of barbiturate drugs should be avoided in the senile group of patients because they frequently produce mental confusion and irritability. The phenobarbital may be combined with a xanthine preparation if desired.

Nitrites. Of the various nitrite drugs which act as vasodilating agents, nitroglycerin (glyceryl trinitrate) has proved the most valuable and most effective in the relief of anginal pain. The size of the tablets recommended should be the smallest which affords the patient relief and this may be 1/200, 1/150, or 1/100 grain (0.3 mg, 0.4 mg, or 0.6 mg). It is necessary to instruct the patient in the use of nitroglycerin and not merely present him with the prescription. When anginal pain occurs, the tablet should be crushed with the teeth and then allowed to melt under the tongue. Fear of drug habituation prevents many patients from using nitroglycerin properly. Each patient may be advised that there is no evidence to indicate that repeated use as needed will lessen the effectiveness or produce dependence. When anginal pain occurs with unavoidable exertion, such as with the strain of defecation or with meals, the patient [illegible] with regard to nitroglycerin should be the avoidance of repeated doses during a single [illegible]

ischemia. Amyl nitrite perles (0.2 cc) are faster in their action than nitroglycerin but are less convenient to handle and are more likely to cause disagreeable throbbing pain in the head and giddiness. Patients who have [illegible] doses or erythrityl tetranitrate in 30 to 60 mg doses three to six times daily. In our experience they have not been of appreciable value.

Xanthine Drugs. An extraordinary amount of controversy exists concerning the value of the xanthine preparations in the treatment of angina pectoris (Boyer, Harper). The intravenous injection of aminophylline (theophylline ethylenediamine) and theophylline with sodium salicylate has been demonstrated to enhance temporarily the tolerance of patients with angina pectoris to exercise and anoxia without pain (Bakst et al). Clinically it seems to us that aminophylline in doses of 3¾ or 7½ grains (0.25 or 0.5 gm) given slowly intravenously once or twice daily is a valuable adjunct for patients who have severe coronary insufficiency as manifested by angina decubitus. Combining aminophylline with 250 cc of 20 per cent glucose also can be recommended. Beneficial effects in similar patients occasionally may be obtained with the use of rectal

tories containing 7½ grains of aminophylline The oral use of aminophylline which may be given in doses of 0 1 to 0 2 gm theobromine calcium salicylate in doses of 0 5 to 1 0 gm or other similar xanthine preparations is probably of little or no value and may produce gastric irritation and insomnia in some cases The use of such preparations therefore must remain optional and if a trial fails to produce improvement continued use seems unwise and uneconomical

Papaverine Papaverine hydrochloride occupies somewhat the same status as the xanthine drugs in the therapeutic armamentarium of patients who have angina pectoris In animals it has been demonstrated to increase coronary blood flow (Essex et al) There is quite general agreement that the intravenous administration of papaverine hydrochloride in doses of ½ to 1 grain (32 to 65 mg) is of value in relieving the pain of acute coronary insufficiency The value of papaverine hydrochloride when administered orally is questionable It may be recommended in doses of 1½ to 3 grains (100 to 200 mg) three or four times daily to patients with angina decubitus or patients with coronary insufficiency with impending infarction There is some evidence that it produces a quinidine like action in preventing auricular and ventricular extrasystoles and lessens the hazard of ventricular fibrillation especially after myocardial infarction Unpleasant side effects such as drowsiness vomiting and disturbances in cardiac conduction may occur

Other Medications Several additional drugs have been favored in recent years because they were considered beneficial for coronary disease Among these might be mentioned testosterone propionate (Luft and Malmstrom Lesser) and vitamin E (tochopherol) (Shute et al Vogelsang) In both instances early enthusiasm concerning the ability of these drugs to improve coronary circulation has not been verified by more critical evaluation (Levine and Likoff Levine and Sellers) Consequently until further investigation has been undertaken they cannot be recommended Chemical thyroidectomy through the use of derivatives of thiourea has offered another medical approach founded on the beneficial effects originally reported in some patients with angina following total thyroidectomy The benefits which have been claimed have been attributed to the lowering of the level of metabolism and thus to the reduction of the demands on the heart muscle and the decrease in the sensitivity of the myocardium to epinephrine (Ben Asher Reveno Schoenewald) Both thiouracil (0 4 to 0 6 gm) daily and propylthiouracil (100 to 150 mg) daily have been found to reduce the basal metabolic rate and to decrease the frequency of anginal seizures in a number of patients There are few cardiologists however who are enthusiastic about this mode of treat

(1) lessen the demands on the heart muscle (2) improve the vascularization of the myocardium and (3) relieve the pain of angina pectoris

Total thyroidectomy by surgical means has been done in an attempt to accomplish the first of these aims but this method of treatment has been abandoned even by its original proponents

Improvement of cardiac vascularization has been attempted through grafting vascularized tissue, such as muscle fat or omentum onto the myocardium by producing an adhesive pericarditis with talc and by ligation of the great coronary vein (O Shaughnessy Beck Thompson and Raisbeck Fauteux) The most recent of these attempts to improve circulation in the coronary arteries has been the anastomosis of a systemic artery to the proximally ligated coronary sinus (Beck et al) All of these procedures entail major thoracic surgery Evaluation of the beneficial results of such procedures when weighed against the risks involved cannot be made at this time yet the recent dramatic advances in the field of cardiac surgery would indicate that further research in this direction may prove fruitful

The surgical attack on the pain of coronary insufficiency is made possible by virtue of the fact that the afferent fibers from the heart enter the spinal cord through the dorsal roots of the upper four thoracic segments after traversing the corresponding sympathetic ganglia Three methods are thus made avail

able (White and Bland) The most used is the injection of the sympathetic ganglia with procaine followed by alcohol In most instances these injections must be bilateral This approach has the advantage of being least traumatic so that it may be attempted in patients for whom the risk of surgery is prohibited This method for the control of cardiac pain should be considered when control of pain proves impossible by medical means alone and frequent anginal attacks recur at rest and lead to physical exhaustion and extreme apprehension The majority of the afferent fibers from the heart pass through the stellate ganglia and stellate block alone has given relief to some patients Paravertebral injection of the first four or five thoracic sympathetic ganglia although a more technically difficult procedure than injection of the stellate ganglia alone has given more consistent relief of cardiac pain Alcohol block has the disadvantage of occasionally resulting in a painful neuritis involving the intercostal nerves More serious complications include pneumothorax and subarachnoid injection of the alcohol with transverse myelitis Thus these procedures cannot be recommended without proper evaluation of the patient s disability and recognition of the risks involved

More certain relief of pain may be accomplished by unilateral or bilateral thoracic sympathetic ganglionectomy or by section of the upper four or five thoracic dorsal roots Excellent relief of pain has been reported through both of these procedures Careful selection of candidates for these procedures is required and the risk involved must be evaluated properly Patients who have congestive failure or recent myocardial infarction should not be considered as likely candidates There seems to be adequate evidence that the fear of removal of a useful warning signal by these surgical procedures is without justification Patients who have had the pain pathways interrupted experience dyspnea pain in the jaw or other manifestations when they are exceeding the limits of their coronary circulation

Summary The fact that treatment for the patient with effort angina must be an individualized regimen should be emphasized again The primary goal at present must be to utilize to the best advantage the coronary supply that is available and to institute those measures which in our present knowledge seem to encourage the development of additional coronary flow through collateral channels For the most part medication plays an insignificant role in the management of these patients Except for mild sedation for the nervous or emotionally tense individual and the use of nitroglycerin when necessary for relief of anginal distress medication is of little proved value Prescribing a number of pharmaceutical preparations is more likely to reflect the physician s enthusiasm for the drugs than his understanding of their expected effect The physician who is able to instruct his patient in the need for mental and physical self control with the avoidance of fatigue and who can instill respect for the need of moderation in habits of work and play without arousing unwarranted fear and self concern will prove more successful in delaying the progression of coronary insufficiency than the physician who has undue enthusiasm for the beneficial effects of the large number of pharmaceutical preparations available for the treatment of the anginal patient

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Robert L Parker

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ACUTE MYOCARDIAL INFARCTION

Acute myocardial infarction is the mos serious and most common cardiac emer gency "Coronary occlusion," "coronary *thrombosis*," and "*acute myocardial infarc* tion" are not synonymous terms Pathologically, acute myocardial infarction occurs frequently without a fresh thrombosis being demonstrable in the coronary arteries Atherosclerotic and thrombotic occlusion likewise may be found in the coronary arteries with*out associated* infarction *of the myocardium* Therefore, the term "acute coronary insufficiency with myocardial infarction" should be generally adopted to designate the cardiac syndrome characterized by prolonged anginal pain, associated systemic reaction and electrocardiographic evidence of acute myocardial injury

Except for the relatively rare occurrence *of embolic occlusion of the coronary arteries*, myocardial infarction presupposes underlying coronary atherosclerosis Unfortunately, too often, acute myocardial infarction may be the first clinical indication of the presence of coronary atherosclerosis

Until the cause of coronary atherosclerosis *is more fully understood, preventive therapy* will not be effective The patient approaching his 50th year, especially if the presence of hypertension is discovered, should be advised regarding the necessity of moderation of his habits of work and play *Poor dietary* habits should be corrected, and the impor*tance of avoiding obesity* should be stressed He should discontinue strenuous physical activities which lead to dyspnea and physical exhaustion, and he should adopt more lei surely hobbies and exercises Gradual transfer of more *responsibility to subordinates* and the taking of frequent short vacations should be encouraged to reduce nervous tension and associated fatigue states The use of tobacco, especially in excess, should

be discouraged The presence of a pre existing anginal syndrome is more likely to lend emphasis to the necessity of these alterations

including rest in bed, the use of coronary vasodilating drugs, sedation, and, when feasible, anticoagulant therapy with di cumarol

Aims in the Therapy of Acute Myocardial Infarction The first aim of therapy in cases of myocardial infarction is the relief of pain and the avoidance of shock The second aim of therapy is directed toward the improvement of nutrition of the ischemic myocardium Because of the occlusive process cardiac nutrition is partially or com pletely interrupted in a segment of the myocardium While it has been assumed that further embarrassment to the myocardium may occur from reflex vasoconstriction of the coronary arterial tree recent experimental work on animals has indicated the ab sence of such a mechanism (Opdyke and Selkurt) To assume an absence of reflex vasoconstriction in the human being with acute occlusion and that it does not play a significant role in the acute pain of myo cardial infarction seems hardly in accord with clinical experience The third aim in the therapeutic attack is to reduce the work of

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the various complicating phenomena

General Consideration of Treatment The suspicion that acute infarction of the myocardium is present is the first indication for instituting proper therapy It is wiser to err by instituting proper treatment for acute myocardial infarction while the diagnosis is temporarily in doubt than to delay until clinical findings establish the diagnosis be yond question An attack of severe anginal pain persisting for 30 minutes or longer, par ticularly if spontaneous in origin and associated with weakness and perspiration, indicates the need for inaugurating therapy until electrocardiographic or other laboratory evidence proves or disproves the pres ence of myocardial infarction

It is not advisable to establish a definite routine for the management of all patients with acute myocardial infarction since treat ment must at all times be individualized We might, however, consider certain measures which are indicated during the acute phase in most instances of acute coronary insuffi ciency with myocardial infarction

Relief of pain is the first requirement Although one of the newer synthetic preparations may be tried, clinical experience would indicate that morphine is the most satisfactory drug for this purpose At least ¼ to ½ grain (15 to 30 mg) of morphine sul fate, administered hypodermically, is usually required and is best combined with 1/150 to 1/75 grain (0 4 to 0 8 mg) of atropine sulfate The administration of morphine should be followed by the intravenous ad ministration of either 7½ grains (0 5 gm) of aminophylline or 1 grain (0 065 gm) of papaverine hydrochloride Both of these

controlled when the patient can be hospital ized Transportation to the hospital is usually more feasible after the pain has been brought under control with sufficient opiate and after restlessness and apprehension have been relieved Transportation by ambulance should be arranged for when this is possible The patient should be kept warm and in the position which he finds most comfortable Except in those cases in which the picture of peripheral shock is dominant the patient is usually most comfortable with the head of the bed moderately elevated Additional opiates may be required after the patient has been admitted to the hospital, but a word of caution is in order against the insistence of deep narcosis beyond that required for the relief of pain and restlessness

There is some difference of opinion re garding the advisability of oxygen inhalation for all patients even when shock, cyanosis, or dyspnea is not present If the patient can be assured under such circumstances that oxygen is being prescribed as advisable medication and does not reflect a moribund state, he will usually co-operate and find comfort in the cool atmosphere of an oxygen tent If he prefers, an oxygen mask may be used Although clinical evidence of anoxemia may not be present, there is probably suffi cient theoretical advantage in maintaining a

high oxygen saturation of the arterial blood to advise the use of oxygen during the first few days in all cases (*Barach and Levy*)

Brief questioning of the patient or his relatives will usually determine whether or not there has been an *antecedent history* of bleeding peptic ulcer renal disease or hepatic disease which would contraindicate anticoagulant therapy *Laboratory procedures* which should be performed immediately include urinalysis and determination of the concentration of blood urea In the absence of contraindication which will be considered in detail later and if laboratory facilities are available for the accurate determination of the prothrombin time anticoagulant therapy should be started at once

General Therapeutic Measures *Rest* Physical and mental rest must still be considered of prime importance in the treatment of myocardial infarction to allow the myocardium to maintain circulation at as close to basal conditions as possible In our opinion the duration of rest in bed and the degree of limitation while the patient is in bed must be individualized depending on the severity of the attack and the presence or absence of complications During the first 2 weeks the patient should not be disturbed by frequent or vigorous physical examination It is possible to examine the heart most of the lungs and the abdomen gently without disturbing the patient This cursory type of examination usually is adequate for following the course of the illness Examinations such as pelvic and rectal examinations which may cause pain and psychic disturbances should be deferred Mental rest during the first week can be abetted by preventing visits to the patient except by immediate members of the family whose visits should be brief The extreme degree of limitation of activities which has been recommended in the past for the patient with acute myocardial infarction is probably not too well founded Certainly the patient with precarious cardiac compensation and severe systemic symptoms should not be permitted to exert unnecessary muscular effort Such a patient should be fed and turned in bed by the nursing staff and should be given sufficient sedative to ensure rest during the first week or two when his condition is most critical It is unwarranted, however, to prevent the patient whose occlusive process is not accompanied by shock prolonged pain or severe systemic reaction from feeding or turning himself The anxiety created in such a patient by complete immobilization may increase cardiac work to a greater extent than permitting him to do a few things for himself It should however be firmly stressed that he is to remain in bed during this acute phase Co operation in this regard is best obtained by a frank explanation concerning the softened myocardium which requires time to heal by fibrosis

The duration of rest in bed will vary with the severity of the illness and the progress of recovery Probably the minimal period of rest in bed should be 3 weeks even in the case in which clinical reaction is mild the course is uncomplicated and serial electrocardiograms reveal rapid evolution toward normal The majority of patients with severe myocardial infarction which is uncomplicated by extension of the infarction arrhythmia or congestive failure should rest in bed for 4 to 6 weeks By this time the sedimentation rate of the erythrocytes usually has reached normal and the electrocardiograms show stabilization with a relic pattern When the course is complicated by recurrent infarction pulmonary embolism or by the development of cardiac decompensation it may be necessary to prolong the period of rest in bed for several additional weeks Elderly persons should be allowed to sit up and the period of strict immobilization should be made as short as possible to ward off the occurrence of hypostatic pneumonia and other similar geriatric complications From the foregoing consideration it is apparent that no set rule can be established concerning the recommended duration of rest in bed Recently in contrast with the conservative treatment in general use there has been a trend toward shortening the period of rest in bed In our opinion a compromise between these two views has proved to be most satisfactory

When the period of restriction in bed for a specific patient is believed to be completed his return to more activity must be gradual At first he is permitted to sit in a comfortable chair for 15 to 30 minutes two or three times a day The patient should be observed carefully during this change in his routine The

appearance of excessive tachycardia or recurrence of definite anginal distress or dyspnea would indicate that further rest in bed is probably advisable If he tolerates sitting up without incident its duration can be extended daily so that, in the course of a week, he may be able to be up several hours daily and may take a few steps about his room When he has regained sufficient strength to be able to walk about the room and change from a lounge chair to his bed unaided and with ease convalescence usually can be safely continued at home

DIET It is generally agreed that ingestion of food increases cardiac work Experimental observation would indicate that distention of the stomach aggravates coronary insufficiency, probably by reflex coronary vasoconstriction This physiologic observation and also the relative frequency of nausea vomiting and abdominal distention immediately following an acute myocardial infarction warrant consideration of dietary management During the immediate acute episode when shock pain and nausea and vomiting may be present, only liquids may be tolerated As improvement occurs usually within the first week a soft diet is substituted with the precaution that feedings should be small Subsequently the caloric value of the diet will vary with the state of nutrition of the patient During the first week the intake in any case should not be more than 1200 to 1500 calories per day In cases in which the patients are obese, a daily diet of 1000 calories is advisable during hospitalization and during the subsequent convalescence until the weight of the patient has been reduced to normal Vitamin supplements such as one of the multiple vitamin preparations should be taken daily while the caloric intake is restricted When obesity is not a problem and when the convalescence is proceeding without incident a general diet should be allowed with no restriction of particular foods except those which may be classified as gas producing foods and those known to be poorly tolerated by the patient Portions

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Drug Therapy OPIATES As previously indicated morphine sulfate has proved to be the most satisfactory of the various opiates for relief of the severe pain of acute myocardial infarction Persistence of intense pain is not only unbearable to the patient but also may be a factor in producing reflex coronary vasoconstriction as well as shock (Kistin and Mazer) A hypodermic injection ¼ grain (15 mg) or more of morphine sulfate usually will be required to control the pain This may be repeated in 30 minutes if necessary and thereafter at intervals of 3 or 4 hours if pain is not relieved In some cases the intravenous administration of morphine may be indicated In place of morphine ¼ to ½ grain (15 to 30 mg) of pantopon (a preparation containing the total opium alkaloids in the form of soluble hydrochlorides) may be administered hypodermically or 1/32 to 1/16 grain (2 to 4 mg) of dilaudid hydrochloride may be given by the same method

The use of opiates in the treatment of myocardial infarction has been criticized on the basis that these drugs may increase vagus spasm depress respiration and cause abdominal distention *Undoubtedly the greatest* disadvantage of morphine sulfate and related drugs is the production of vomiting in sensitive persons Such an unfavorable reaction may be avoided by questioning the patient or members of the family about previous undesirable reactions to opiates If the patient has had such a reaction one of the newer synthetic analgesics may be substituted

ministered intravenously or intramuscularly The oral administration of papaverine hydrochloride has been advocated to prevent cardiac irritability but whether the drug produces any significant benefit when given orally is open to question We believe papaverine hydrochloride has a definite place in the immediate treatment of acute coronary insufficiency Frequently when it is administered slowly by the intravenous route it produces dramatic relief from the crushing pain and may make the use of other opiates unnecessary It certainly should be given in preference to morphine when there is a history of previous unpleasant reactions from morphine sulfate The administration of papaverine hydrochloride may be repeated in 30 minutes if there is recurrence of pain The

tiously or not at all in the presence of peripheral vascular collapse When papaverine hydrochloride is given too rapidly vomiting and hypotension may occur consequently slow administration is necessary

XANTHINE DRUGS In our opinion the oral administration of xanthine preparations such as aminophylline theobromine sodium acetate or theobromine calcium salicylate is of little or no value for the patient with acute myocardial infarction Aminophylline (theophylline ethylenediamine) administered intravenously however is effective in increasing coronary blood flow and is a valuable preparation In the event of prolonged pain and also in the presence of nocturnal dyspnea or pulmonary edema this drug deserves adequate trial It should not be injected rapidly It may be given in doses of 3¾ to 7½ grains *(0 25 to 0 5 gm) either alone or in combina*tion with 100 to 200 cc of 20 per cent solution of dextrose by intravenous drip Either aminophylline or papaverine hydrochloride

in the event of recurrent anginal pain As previously stated aminophylline and papaverine should not be given simultaneously

BARBITURATES Sedation with barbiturates is indicated during convalescence from myocardial infarction in order to insure sleep and to suppress anxiety Phenobarbital may be administered orally in doses of ¼ to ½ grain (0 016 to 0 032 gm) two or three times a day as needed to assist the patients to relax *while they are awake It is unwise* however to administer sedatives in doses larger than necessary to produce relaxation The tendency of some physicians to keep patients with acute infarction "snowed under" for days is to be deplored Caution must also be used in prescribing barbiturates to aged patients

owing to the tendency of these drugs to produce confusional states

ATROPINE SULFATE It is not entirely agreed how effective neurogenic mechanisms are on the coronary vessels and coronary blood flow in man The results of various experimental studies in animals are not in agreement Some cardiologists advocate the use of atropine sulfate by hypodermic injection in repeated doses during the first few days of acute myocardial infarction It is assumed that this drug, by inhibiting vagal action, suppresses reflex vasoconstrictive impulses to the coronary arteries and also prevents dis

tachycardia, we are not enthusiastic about its use except in accompaniment with hypodermic injection of opiates for the relief of pain We prefer to administer quinidine sulfate when there is indication of increased myocardial irritability

ALCOHOL Whisky or brandy may be prescribed in small amounts especially for patients who are accustomed to the use of alcoholic beverages Patients who note residual thoracic discomfort after the severe anginal pain has subsided may be benefited by alcohol It has the beneficial effects of alleviating apprehension and promoting relaxation

NITRITES During the acute phase of myocardial infarction glyceryl trinitrate, amyl nitrite, and the other nitrites are of little value in relieving pain Their repeated administration in the presence of suspected infarction should be avoided because of their tendency to produce hypotension and to increase shock

ANTICOAGULANT THERAPY Experience in the past few years regarding the use of anticoagulants has without exception served to emphasize the value of dicumarol in the treatment of patients with acute myocardial infarction The high incidence of thromboembolic complications as an aftermath of acute myocardial infarction has been one of the main factors in contributing to a high mortality and high morbidity rate (Nay and Barnes) These complications result from secondary thrombotic occlusions in the coronary arterial tree with extension of infarction, mural thrombus with arterial emboli, thrombophlebitis with pulmonary embolism, and in situ thrombosis of other arteries already affected by atherosclerosis Anticoagulant therapy, effectively controlled, will certainly reduce the hazard of complication of this type Recent investigations have shown that dicumarol does not adversely affect myocardial repair after infarction and does not cause an increase in myocardial hemorrhage or necrosis (Blumgart et al) Apprehension in this regard has previously caused some physicians to be reluctant to employ anticoagulant therapy The same apprehension has been expressed concerning the role of subintimal hemorrhage in the production of acute arterial occlusion with secondary thrombosis Pathologic studies have shown that small hemorrhagic areas occur not infrequently in the subintimal atheromatous plaques of coronary vessels affected by atherosclerosis Actual closure of the arterial lumen by free bleeding into one of these areas resulting in displacement of the intima is not common One might well anticipate finding this type of lesion particularly in cases of fatal acute infarction in which anti

the enthusiasm for anticoagulant therapy

There are two preparations available for producing an anticoagulant effect on the blood The administration of both of these preparations requires supervision Neither preparation possesses the qualities which one would desire in an ideal anticoagulant Heparin is expensive and its effect is of brief duration It, therefore, has to be administered continuously or at frequent intervals by the

more difficult to control and it may cause bleeding at the site of injection It is seldom justifiable to administer heparin for more than a few days and, fortunately, this is not necessary when it is administered with dicumarol

Dicumarol is inexpensive and also has an other advantage, that is, it can be administered orally It also has some disadvantages Daily determinations of the prothrombin time are necessary to control the dosage of this drug Another disadvantage is th

effect is delayed for 24 to 72 hours after its administration is started and the effect may persist for from 2 to 7 days after administration of the drug is discontinued Furthermore there is a wide variation in the sensitivity of patients to dicumarol To be effective the dosage of the drug should reduce the prothrombin activity to between 10 and 20 per cent of normal and should maintain it at this level When the dosage is properly controlled the risk of bleeding is negligible but the possibility of this complication should always be kept in mind Major bleeding can usually be controlled promptly by intravenous administration of 60 mg of synthetic vitamin K and by the transfusion of fresh citrated whole blood

Are both heparin and dicumarol necessary in the usual case of acute myocardial infarction? This question has not been satisfactorily answered as yet by clinical experience The only justification for employing heparin in addition to dicumarol is to obtain the immediate anticoagulant effect which heparin produces and to continue this effect until dicumarol produces an optimal decrease of the prothrombin activity How necessary is it then to obtain an immediate anticoagulant effect during the 1 to 3 days before dicumarol becomes effective? It has been shown that thrombo embolic complications seldom occur before the fifth day after the onset of acute myocardial infarction Thus in most instances dicumarol alone should be sufficient Because of the greater likelihood of an extension of the thrombotic process in the coronary arterial tree or other vascular complications in those cases of myocardial infarction in which the clinical picture is one of shock with marked hypotension and slowing of circulation and hemoconcentration it would seem justifiable to use heparin for its immediate effect in addition to dicumarol In cases of acute coronary occlusion in which this profound systemic reaction does not occur and in cases in which patients enter the hospital several days after the onset of clinical evidence of acute infarction heparin is probably not necessary

Contraindications to Administration of Dicumarol The first contraindication to dicumarol therapy is lack of proper laboratory facilities for accurate determination of the prothrombin time Emphasis must be placed on the fact that it is not safe to initiate treatment [illegible]

In cases in which renal and hepatic insufficiency are present the effect of dicumarol may be greatly accentuated and difficult to control therefore dicumarol therapy should be omitted (We have found it advisable to examine the urine and to determine the concentration of blood urea before starting the administration of dicumarol A slight elevation of the value for the blood urea does not contraindicate the administration of dicumarol but it is wise under such circumstances to reduce the initial dose to 100 or 200 mg until the patient s sensitivity to the drug can be determined) A history of peptic ulcer or known ulcerative lesion of the gastro intestinal tract should preclude its use and it should be avoided in purpura or blood dyscrasia It should be used with caution in those cases in which the diet has been markedly restricted for several days and in cases in which prolonged nausea and vomiting have caused a definite nutritional deficiency In such cases the patients frequently are hypersensitive to the drug

Administration of Anticoagulants In the majority of cases of acute myocardial infarction we have not felt it advisable to give both heparin and dicumarol except under the circumstances previously mentioned If both heparin and dicumarol are to be used the following schedule may be suggested 300 mg of dicumarol are given orally when the patient is admitted to the hospital or as soon as the clinical diagnosis of acute coronary occlusion has been made and contraindications to the administration of the drug have been excluded At the same time 50 mg of heparin are given intravenously and repeated at intervals of 4 hours * The prothrombin time is determined every morning If there is only a negligible increase in the prothrombin time on the morning after the administration of the initial dose 200 mg of dicumarol may then be given If however the prothrombin time indicates a drop in the

* A new form of depot heparin is now available 200 mg are administered intramuscularly once or twice in 24 hours depending on the coagulation time as determined by the Lee White method.—*Editor*

level of prothrombin activity to approximately 50 or 30 per cent of normal, the administration of dicumarol is omitted on the second day in order to avoid an undue suppression of prothrombin activity in what *would appear to be more than a usually* sensitive patient The administration of heparin is discontinued when the prothrombin time taken 3 hours after the last injection of heparin indicates that the prothrombin activity is 30 per cent of normal Subsequent to the second day, 50 to 200 mg of dicumarol are given orally on those days on which the prothrombin time indicates that the prothrombin activity is greater than 20 per cent of normal and the administration of the drug is omitted on those days on which the prothrombin activity is less than 20 per cent of normal In some cases a dose of 200 mg may have to be administered daily to maintain the prothrombin time at the desired level In other cases this effect may be obtained by [illegible]

[illegible] age by daily determination of the prothrombin time

It has been our policy to continue anticoagulant therapy as long as the patient is confined to the hospital Although theoretical considerations would strongly suggest continuation of this therapy throughout the convalescent period it has not been practical as yet to carry out a program of this type Perhaps further investigation will result in the development of an anticoagulant which is as effective as dicumarol but which is more easily controlled Although a decrease of the prothrombin activity to almost zero (prothrombin time of 70 to 100 seconds when 60 seconds represent prothrombin activity that *is 10 per cent of normal) is rarely associated* with bleeding manifestations such a decrease is a cause for concern When it is encountered, 25 to 72 mg of menadione bisulfate [illegible]

[illegible] dosage, dicumarol and when advisable, both heparin and dicumarol has resulted in the most significant single advance in recent years in the treatment of impending coronary occlusion as well as in the treatment of acute myocardial infarction

Complications of Myocardial Infarction Shock Profound shock in association with myocardial infarction usually denotes a poor [illegible]

[illegible] cardium and diminished cardiac output In many cases, the symptoms of shock will be alleviated by the administration of oxygen plus the relief of pain by measures outlined previously Whether or not treatment of shock by increasing circulating blood volume is indicated when the primary disturbance is myocardial in origin remains a debatable point In our experience the slow administration of 300 to 500 cc of plasma or whole blood by the intravenous route occasionally has been of definite value in patients with profound shock

Cardiac Arrhythmia *Extrasystoles* The occurrence of frequent extrasystoles, particularly if they can be demonstrated to arise from the ventricular myocardium, may portend ventricular tachycardia or fibrillation Administration of quinidine sulfate in doses of 3 grains (0 2 gm) three or four times daily is indicated under these circumstances and will in most instances abolish these signs of cardiac irritability We have not found it advisable to use quinidine routinely unless evidence of cardiac irritability was present

Ventricular Tachycardia This is an ominous complication which may lead to sudden death from ventricular fibrillation Therapy with quinidine sulfate should be adequate [illegible]

[illegible] (0 4 to 0 6 gm) every 2 hours until the tachycardia terminates or until quinidine intoxication occurs If the attack terminates as a result of this therapy, 3 grains (0 2 gm) of quinidine sulfate should be administered four times daily during convalescence

Auricular Fibrillation and Auricular Flutter In the absence of congestive heart failure,

the development of auricular fibrillation or auricular flutter likewise warrants an attempt to convert the arrhythmia to sinus rhythm with quinidine alone Even though normal rhythm is re established administration of quinidine

congestive heart failure with pulmonary con gestion and retention of fluid may occur even while the patient is at complete rest This *unfortunate complication indicates* severe damage to the myocardium and poses a dif ficult therapeutic problem The intake of sodium should be restricted when there is evidence of retention of fluid A diet with sodium content of 0 5 gm is satisfactory The appearance of basal pulmonary rales should be a warning that acute pulmonary edema is *likely to* develop Pulmonary congestion is benefited by the slow intravenous injection of 7½ grains (0 5 gm) of aminophylline (theophylline with ethylenediamine) in 200 cc of a 20 per cent solution of dextrose two or three times daily Oxygen in high concen trations is of value in relieving dyspnea it *preferably should be used before pulmonary* edema occurs The intravenous or intramus cular injection of one of the mercurial diuretics in the usual doses may be of value when there is evidence of retention of fluid but should be avoided when there is marked hypotension with a low output of urine *When* acute pulmonary edema occurs mor phine should be given in addition to oxygen and aminophylline

In spite of these measures it may be im possible to maintain cardiac compensation without the use of digitalis Traditionally digitalis has been considered to be contrain dicated in cases of acute myocardial infarc tion because of the fear that it might cause myocardial rupture ectopic rhythm and ent study duce car ut that it was likely to increase the incidence of thrombo embolic phenomena (Askey and Neurath) The latter complication can now be largely avoided by the use of dicumarol In our opinion it is most unwise to withhold *digitalization* when it becomes obvious that congestive failure cannot be controlled with out it

Digitalis should be administered orally *unless rapidly progressive* acute pulmonary edema necessitates intravenous administra tion The preparation of choice should be the one with which the attending physician has the most experience Digitoxin or one of the purified glycosides is usually recommended An initial oral dose of 0 6 mg of digitoxin *should be followed in 8 to 12 hours by a dose* of 0 4 mg Subsequently 0 1 to 0 2 mg should be administered daily unless there is evidence that this dose is insufficient or excessive

Diabetes Mellitus Glycosuria may occur as a transitory finding during acute myocar dial infarction and as such does not denote that diabetes mellitus is present Knowledge of this occasional finding is of importance because the administration of insulin for such glycosuria is unnecessary and may be haz ardous Myocardial infarction in a diabetic patient will require careful supervision of the diabetes It is essential to avoid hypoglycemic reactions and it is wiser to permit moderate hyperglycemia and slight glycosuria to de velop during the first few weeks of myocar dial infarction than to entail the risk of *hypoglycemic reactions*

Shoulder Hand Syndrome One of the most baffling complications which is fre quently encountered in patients recovering from acute myocardial infarction is unilateral or bilateral painful fixation of the soft tissues of the shoulders which often is associated in on et al) It can best be classified as a neurocircu *latory dystrophy It is commonly called* the shoulder hand syndrome" Treatment has been of two main types First conservative management with heat gentle massage and passive exercises should be tried The failure of conservative measures to give relief and the continuation of severe pain warrant in terruption of the sympathetic innervation by injection of procaine hydrochloride into the stellate ganglion or of the first three or four thoracic sympathetic ganglia Repeated *block by this means may be necessary* and sympathectomy may be necessary in some cases

After Care of the Patient The after-care of the patient who has recovered from the acute phase of myocardial infarction consists

primarily of an individualized guidance program to return the patient to a useful and productive life Certainly, the rest program should be continued after the patient leaves the hospital Generally, the patient should remain at home for from 4 to 8 weeks after he leaves the hospital Patients seldom should be permitted to return to work, even on a part time basis, in less than 12 weeks, even though the work is of a sedentary type Resumption of increasing hours of work and responsibilities should be gradual, and the necessity for assuming a lowered level of activity and a less competitive philosophy of life should be emphasized Just as important is the necessity for reassurance and optimism that an enjoyable and productive life is possible Whether or not an anginal syndrome develops after recovery from acute infarction adequate daily rest is important The patient should be advised to obtain at least 9 hours of rest in bed each day and to continue a daily rest period of an hour or two each afternoon The avoidance of both nervous and physical fatigue and continued moderation in eating, drinking, and smoking also should be emphasized

The degree of physical disability following the recovery phase of acute myocardial infarction will, of course, vary greatly One patient may be completely incapacitated with little evidence of myocardial reserve, whereas another patient may have little symptomatic or objective evidence of impaired cardiac function Obviously, guidance in each case will have to be individualized depending largely on the physician's judgment of the existing cardiac reserve

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SUBACUTE BACTERIAL ENDOCARDITIS

Until the introduction of penicillin the treatment of subacute bacterial endocarditis was inadequate and discouraging It was esti mated that at most 1 per cent of the cases had a spontaneous remission With the ad vent of the sulfonamides the rate of cure rose to between 4 and 6 per cent The use of the sulfonamides with heparin and with hyperthermia was said to result in a some what higher rate of recovery However at best only 10 per cent of patients survived

With the use of penicillin the outlook for these patients changed radically As soon as adequate amounts of penicillin were avail able reports of cures began to appear in the literature in approximately 70 to 80 per cent of cases

Etiologic Organisms In the treatment of subacute bacterial endocarditis it soon be came evident that the type of organism and its susceptibility to antibiotics were of the greatest importance In the earlier cases most successful results were usually obtained when the organisms were extremely sensi tive to penicillin However it soon became apparent that resistant organisms could be adequately handled by using large amounts of penicillin

Fortunately approximately 90 per cent of cases are caused by the alpha streptococcus (viridans) This organism is usually ex tremely sensitive to penicillin Seven per cent of cases are caused either by the gamma streptococcus the beta hemolytic strepto coccus the enterococci or a nonhemolytic streptococcus (the streptococcus s b e) As a rule the organisms in this group are rela tively insensitive The remainder of cases have as their etiologic agent a gram negative bacillus such as the influenzal organism and a variety of other bacteria These organisms are usually insensitive to penicillin but may be quite susceptible to streptomycin to a sulfonamide to aureomycin or chloromy cetin

Isolation and Determination of Char acteristics of Organism In treating sub acute bacterial endocarditis the first step is culture of the organism or organisms in volved Occasionally in a particular case more than one organism is the cause of the disease The sensitivity to penicillin must be determined for all organisms Of the vari ous methods in use the serial dilution test are probably as quick and as satisfactory in obtaining significant results with a minimum of errors In each case a control is made with a standard strain of *Staphylococcus au reus* of known sensitivity (*Staphylococcu aureus* HMB 109) The usual bacteriostatic level of a penicillin sensitive organism is 0 01 to 0 1 oxford units per cubic centimeter A range up to 1 0 oxford units per cubic centi meter is considered moderately sensitive Anything above 1 0 must be considered rela tively penicillin resistant If the organism shows an in vitro sensitivity to penicillin greater than 1 0 oxford units per cubic centi meter its resistance to streptomycin aureo mycin chloromycetin and to sulfadiazine should be determined

Treatment should not be initiated until the responsible organism or organisms have been identified and tested It is best to ob tain at least two positive cultures While it is desirable to begin treatment as soon as pos sible the slight additional risk of delay will usually be more than offset by the essential therapeutic information gained from the culture and sensitivity studies The only ex ceptions to the above rule are patients who are practically moribund and patients in whom the clinical diagnosis is unequivocal although multiple cultures of the blood have been negative In the latter case cultures using increased carbon dioxide tension and anaerobic conditions should be utilized Oc casionally bloods drawn 5 15 and 30 min utes after the subcutaneous administration of 0 5 cc of 1 1000 adrenalin will help in obtaining a positive culture This procedure is contraindicated in patients with hyper tension coronary artery disease or severe congestive heart failure Arterial blood and sternal marrow cultures may be positive when venous blood cultures are negative Blood drawn during febrile periods is more likely to give positive results Cultures should be incubated for at least 2 to 3 weeks before being called negative Samples of positive cultures should be kept for the duration of the treatment

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day The second is how long should treatment be continued If continuously high penicillin plasma levels are maintained for a sufficiently prolonged time success will be achieved in a large majority of cases

The plasma penicillin level should be kept five to ten times higher than the in vitro sensitivity of the organism It has been shown that the minimal in vivo bacteriostatic level is at least four times the in vitro sensitivity The reason for this has not been clearly established Possibly the higher levels are needed to penetrate into the fibrin of the vegetative processes in order to inhibit the bacteria therein lodged It must be emphasized that the adequacy of blood levels cannot be judged from the dosage required to clear the circulating blood of organisms This may be accomplished with inadequate doses and may not only fail to cure but may actually result in the development of a more resistant organism

In all cases of resistant organisms and in those cases that fail to achieve a negative culture in spite of having a penicillin plasma level at least five times the in vitro sensitivity of the organism help may be obtained from the following test based on the action of the patient s own serum during penicillin administration on the specific infectious organisms isolated It is similar to the test employed by Rammelkamp for the determination of in vitro sensitivity Two sets of tubes are used Samples of the patient s serum taken 5 minutes prior to the next penicillin injection are put in the tubes of both sets The first set is inoculated with 1 1000 dilution of a 6 hour broth culture of a standard strain of *Staphylococcus aureus* The second set of tubes is inoculated with a

diluent If no growth of the patient s organisms takes place in the undiluted tubes then an adequate penicillin plasma level is present If growth occurs in the undiluted tubes the level is insufficient and the amount of penicillin must be increased

As a rule one can estimate the plasma penicillin level by the amount of crystalline penicillin given This estimate will be altered if there is impaired renal function or sources of inactivation of penicillin and possibly by large fluctuations in daily fluid intake Usually for each million units of crystalline

tinuous intramuscular or intravenous drip If the intermittent intramuscular route is used and depending on the time interval between injections 1,500 000 to 2 000 000 units will be needed to obtain a plasma level of 1 0 oxford units per cubic centimeter With 1 000 000 units of crystalline penicillin a day variations occur so that a plasma level of only 0 5 oxford units per cubic centimeter may be obtained in a patient with normal renal function while if impaired renal function is present the plasma level may rise to 2 0 oxford units per cubic centimeter or more Regardless of how low the sensitivity may be the minimal total daily dose should be 600 000 units In those cases in which cultures have been repeatedly negative but in which the diagnosis has been satisfied by other criteria a minimum of 2 000 000 units of penicillin should be given per day This amount likewise should be used for the rare cases in which the general condition of the patient is too poor to await bacteriologic studies and the patient must have treatment immediately after admission to the hospital

METHODS OF ADMINISTRATION OF PENICILLIN Controversy has arisen in regard to the optimal method of administration of antibiotics With continuous intramuscular or intravenous therapy a more or less constant level may be expected With intermittent intramuscular injection the plasma level will vary depending on the time after injection that the test is run Only a small amount of penicillin will remain in the plasma 2 hours after a single intramuscular injection There has also been discussion as to whether it is

closely as possible a continuous adequate level

If the total daily dose is not greater than 3 000 000 units the intermittent intramuscular route may be used Injections of ⅟₁₂ th the total daily dose should be given alternately in the buttocks and arms every 2 hours day

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Penicillin There are two crucial problems to be answered in every penicillin treated case of subacute bacterial endocarditis The first is the amount of penicillin needed per

day The second is how long should treatment be continued If continuously high penicillin plasma levels are maintained for a sufficiently prolonged time success will be achieved in a large majority of cases

The plasma penicillin level should be kept five to ten times higher than the in vitro sensitivity of the organism It has been shown that the minimal in vivo bacteriostatic level is at least four times the in vitro sensitivity The reason for this has not been clearly established Possibly the higher levels are needed to penetrate into the fibrin of the vegetative processes in order to inhibit the bacteria therein lodged It must be emphasized that the adequacy of blood levels can not be judged from the dosage required to clear the circulating blood of organisms This may be accomplished with inadequate doses and may not only fail to cure but may actually result in the development of a more resistant organism

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and night Hourly injections may be better but offer practical difficulties If 5,000 000 or more units must be given per day, the continuous intravenous drip should be used The total daily dose is dissolved in a liter of either 5 per cent glucose, normal saline, or Ringer's solution Twenty to 40 milligrams of heparin should be added to the liter of solution in order to prevent clotting in the needle and to help avoid local thrombophlebitis at the sites of intravenous infusion The rate of flow is adjusted so that the drip is fairly constant throughout the 24 hours By this method it may be possible to keep one needle in a vein for 7 days or longer If all accessible veins are thrombosed, or if for other reasons intravenous medication is impossible, the continuous intramuscular route may be used However, myositis and fever are more likely to result when the intramuscular route is used In cases extremely sensitive to penicillin, 600 000 units of a prolonged acting

not be used if the in vitro sensitivity of the organism is greater than 02 oxford units per cubic centimeter

Enhancement of Penicillin Levels * In cases requiring penicillin levels greater than 5 0 oxford units per cubic centimeter additional steps may be needed to obtain these values Benzoic acid diodrast, and para aminohippuric acid have been used in the past The latter two have the disadvantage of having to be given intravenously Likewise in the large doses needed there have been some toxic effects For the purpose of

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nontoxic in the required doses and being effective when given orally

It has been shown that 80 per cent of the urinary elimination of penicillin is by tubular excretion and 20 per cent is via glomerular filtration Caronamide effectively blocks the tubular excretion of penicillin by inhibiting the mechanism responsible for the transport of penicillin by excretory tubular cells Caronamide itself is eliminated by glomerular filtration Thus, if large doses of penicillin alone do not result in the expected high plasma levels, or if levels are needed that cannot be reached with 10 000 000 units per day, the oral administration of caronamide is indicated Because the duration of caronamide's action is 4 hours at most, it is necessary to give it orally at least every 3 hours A dose of 3 gm every 3 hours should result in a plasma caronamide level of between 20 to 30 mg per cent Usually this results in a threefold to fivefold increase in the plasma penicillin level However, patients with some impairment of tubular function will need less caronamide to inhibit completely tubular excretion than will patients with normal tubular function Slight nausea and vomiting may occur This is not an indication for stopping the drug Inasmuch as caronamide is precipitated in an acid urine one should maintain a high urinary output or an alkaline urine Because of its relative lack of toxicity it may be given for periods up to 4 to 5 weeks While caronamide is being administered urinary output and blood urea nitrogen should be checked to make certain that no gross alteration has occurred

Duration of Therapy The duration of treatment will vary from case to case No objective tests are available to give a definite answer to this problem Four weeks of continuous therapy is the minimum when the organism is sensitive to penicillin while 6 to 8 weeks is the usual length of treatment when one is dealing with a resistant organism However, in all cases treatment should be continued for at least 3 weeks after subsidence of the patient's main symptoms and after the blood culture has become negative While patients are being treated, blood cultures should be taken at least once a week An antipenicillin agent (penicillinase) should be added to all blood cultures taken while the patient is on penicillin therapy

This will help to inactivate the penicillin in the drawn plasma and thus aid in culturing any bacteria still present in the blood Favorable therapeutic response is indicated by a return to normal of the temperature, pulse rate, gain in weight, an absence of sweats, the beginning recession of splenomegaly and

even in a patient who is responding favorably.

Nonspecific Supportive Therapy In addition to specific antibiotic therapy, supportive measures must also be employed Thus, at the beginning of the treatment, if significant anemia is present, the patient should be given transfusions until a red count of 4 000 000 and hemoglobin of at least 75 per cent are obtained In addition to the obvious benefit to the weakened myocardium, increase in antibody formation will

sory vitamins must be administered if there are evidences of such deficiencies If the patient's condition is such that adequate food intake is impossible, intravenous feedings

the usual manner If congestive failure is present, digitalization and diuretics should be used as for any other patient All foci of infection, especially infected teeth should be removed while the patient is undergoing treatment

The Use of Streptomycin As mentioned earlier there are certain cases that do not

organism is either completely insensitive to penicillin or those which have failed for some reason to respond to maximal penicillin therapy In such cases streptomycin sensitivity tests must be carried out

The number of cases of streptomycin-treated subacute bacterial endocarditis is as yet too small to evaluate properly the in vitro tests of streptomycin sensitivity However, if the sensitivity of the organism is 8 micro

on a regimen of at least 4 to 6 gm of streptomycin per day It should be given in divided intramuscular doses at 3 hour intervals After a single intramuscular injection of streptomycin, relatively high plasma levels are present for approximately 4 hours The drop in concentration is quite rapid after that period It is essential that large doses of the drug be given from the start because bacteria have a great tendency to develop resistance to this antibiotic Plasma levels should be obtained, as in cases treated with penicillin, and an attempt made to reach a level approximately five to ten times that of the in vitro sensitivity After a favorable response treatment should be continued for 4 weeks

Although toxic manifestations, both vestibular and auditory, are quite common when streptomycin is administered in large amounts over a relatively long period (2 to 3 weeks or more), a favorable result calls for the continuation of the drug for a total of at least 3 weeks in spite of these toxic manifestations Audiometric and vestibular function tests should be done before treatment is started and at weekly intervals while therapy is being continued

Aureomycin and Chloromycetin In the past few months, aureomycin and chloromycetin have been added to the field of antibiotics While detailed reports of their use in bacterial endocarditis are yet to appear, they undoubtedly will be of aid in cases due to organisms poorly responsive to penicillin and streptomycin Though these newer antibiotics may be effective against organisms known to be penicillin sensitive, their present use in bacterial endocarditis should be limited to those cases in which they are much more effective against the organism than either penicillin or streptomycin

In general, aureomycin is more active against the coccal organisms than against gram negative bacilli The hemophilus group particularly may be susceptible to aureomycin Organisms such as penicillin resistant streptococci, pneumococci, and staphylococci should be tested for aureomycin sensitivity Effectiveness has been demonstrated against Brucella and most Salmonella

Dosage of aureomycin in cases of bacterial endocarditis is not settled Administration by the oral route is preferred It should be given every 4 hours The sensitivity of the organisms should be determined and a dosage prescribed which will give a serum concentration of at least five times the in vitro sensitivity Following an oral dose of 1 0 gm, serum concentration of 0 6 to 2 5 micrograms per cc are obtained in 2 to 4 hours, and concentrations of 5 to 20 micrograms per cubic centimeter of serum are subsequently maintained during continuous oral administration of 1 gm every 4 hours The minimal amount of aureomycin in bacterial *endocarditis should be 1 gm every 4* hours If in vitro sensitivity studies indicate need for greater amounts the dose may be *increased to 2 gm or more every 4 hours* Serious toxicity from aureomycin has not been reported Gastric irritation which does occur, may be minimized by the administration of antacids or food If the patient's condition precludes oral administration the intravenous route may be used Aureomycin is given intravenously in a dosage one fifth that of the oral dose At least 1 cc of leucine diluent should be used for each 10 mg of aureomycin The sterile solution is injected immediately after preparation over a period of at least 5 minutes Because of the frequency of thrombophlebitis, intravenous administration should be discontinued as soon as the patient is able to take the drug orally Intramuscular therapy *has been too painful* for the prolonged administration of aureomycin

Chloromycetin gives promise of success in the treatment of endocarditis due to Brucella the Salmonella group, and the coli form bacteria These groups though uncommon as a cause of endocarditis, have been among the most difficult to treat Chloromycetin should be given orally as it is well absorbed from the gastro intestinal tract The initial dose is approximately 50 mg per kilogram of body weight Following this 0 25 gm should be administered every 3 hours This schedule should result in a

greater than the usual

ganisms listed as susceptible to chloromycetin Serious toxic manifestations have not been observed

With both aureomycin and *chloromycetin* the duration of treatment of bacterial endocarditis is still to be decided However it is probable that treatment should be continued for at least 2 weeks after subsidence *of the patient's main symptoms* and sterilization of the blood stream Although the potentialities of these newer antibiotics in the treatment of bacterial endocarditis are great it must be emphasized that our knowledge of their use is still in its infancy

that the further valvular accumulation of leukocytes, fibrin, and organisms would be pre*vented The subcutaneous administration of* heparin is painful and the intravenous route is bothersome technically While many of these objections have been overcome by the oral use of dicumarol subsequent experiences of numerous investigators have shown that patients do as well without the anticoagulants which often complicate the treatment Embolization has not been lessened by their use Heparin frequently causes febrile reactions that may obscure the clinical picture Hemorrhages have resulted and an occasional death has been attributed to these drugs If thrombophlebitis or phlebothrombosis occurs as a complication during the treatment of subacute bacterial endocarditis *routine heparin and dicumarol treatment* should be instituted Other than for these uses, anticoagulants have no place in the treatment of subacute bacterial endocarditis

Relapses Occasionally relapses may occur This may be due either to an inadequate plasma level or to the early discontinuance

will kill the more sensitive of the organisms and yet allow certain less sensitive bacteria to multiply The usual time for relapse is 2 *to 4 weeks after the completion of the course*

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ing completion of treatment and the patient should be carefully observed The patient

may be asymptomatic even though the cul ture is positive

In case of relapse the organism should again be tested for sensitivity and another complete course of treatment instituted In other words it must be treated as a newly developed case of subacute bacterial endo carditis It is preferable not to discharge a patient until 4 weeks after the antibiotics have been stopped Careful follow up with frequent blood cultures should be continued for at least a year Only then can the infec tion be considered arrested

Complications The foremost complica tions during therapy are embolization and myocardial failure Occasionally evidence of cerebral meningo encephalitis will be ob served Penicillin idiosyncrasy may be mani fested by a rash or a febrile reaction Usually this may be satisfactorily overcome by

In cases of infected emboli with abscess

acute bacterial endocarditis Myocardial failure per se is not a complication of treat ment It may develop during or be a sequel to the infection It is well known that in subacute bacterial endocarditis minute em boli small infarcts and diffuse inflammatory reaction may be present in the myocardium Structural alterations in the myocardium that occur with healing adequately explain the advent of failure In cases where subacute bacterial endocarditis is superimposed on rheumatic heart disease a reactivation of rheumatic myocarditis frequently occurs Likewise valvular damage may be increased during the processes of healing and further contribute to myocardial failure The earlier the diagnosis of subacute bacterial endo carditis is made and treatment started the less likely is the occurrence of congestive failure Digitalis diuretics and a low salt diet should be used as in the treatment of any case of congestive heart failure

Prophylaxis Perhaps one of the most im portant *items is the prophylaxis of this* disease In all bacterial infections such as pneumonias etc blood cultures should b obtained before the institution of antibioti therapy This is imperative in all cases o previous valvular damage In patients witl known heart disease antibiotics must b given before all elective surgical procedures Particularly important are tooth extraction which result in a 70 per cent incidence o transient bacteremia Tonsillectomies pros tatic operations other genito urinary pro cedures and any surgical intervention ı infected tissues are apt to have subacut bacterial endocarditis as a sequel Therefor it is recommended that such patients receiv an injection of 600 000 units of a prolonge acting penicillin mixture This dose should b given 2 to 3 hours before the procedure an daily for 2 to 3 days thereafter In cases o subacute bacterial endocarditis undergoin therapy a careful search must be made fo all foci of infection and their removal ac complished during the course of treatment

The successful use of antibiotics has al tered the views on surgery for cases of paten ductus arteriosus Formerly one of the prin cipal indications for ligation was the preven tion of subacute bacterial endarteritis A the present time it is felt that other sequelae such as failure of proper growth progressiv *cardiac strain and disability and a dynami* cally large communication should be th determining factors rather than the preven tion of endarteritis

In active cases of subacute bacterial en darteritis the primary consideration shoul be the elimination of the infection by th use of antibiotics Several months after th successful completion of such treatment liga tion may be carried out as an electiv procedure

MILTON GROSSMAN
LOUIS N KATZ

ACUTE BACTERIAL ENDOCARDITIS

In general results of treatment of acut bacterial endocarditis have been disappoint ing Few reports of recovery have appeare in spite of availability of penicillin and strep tomycin It is hoped that the newer antibiotic —aureomycin and chloromycetin—will in crease the survival rate in this disease Ac curate diagnosis at the earliest possibl moment must be stressed Acute endocarditi is characterized by its occurrence in a patien without previous known heart disease by it

short duration, and usually by its fulminating course As a rule, the organisms responsible are the hemolytic streptococcus, the pneumococcus, and *Staphylococcus aureus* In general, the treatment is similar to that of subacute bacterial endocarditis However, one must not temporize even as much as with subacute bacterial endocarditis Blood cultures and organism sensitivity should be obtained and therapy started immediately The principles of therapy are the same as those of subacute bacterial endocarditis Response to treatment should be evaluated within a few days and if a satisfactory result is not being obtained, either the dosage must be increased or an additional antibiotic be given

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ACUTE MYOCARDITIS OF INFECTIOUS DISEASE

Modern clinicians are becoming increasingly aware of the fact that acute infections other than rheumatic fever and diphtheria are capable of producing acute myocarditis Recent contributions to the medical literature emphasize that cardiac manifestations of acute infectious diseases occur more frequently than are commonly recognized Mild infections of the upper respiratory tract such as nasopharyngitis and tonsillitis may produce an acute inflammation of the myocardium which unless carefully sought may escape detection Frequently the cardiac symptoms and findings do not appear until the primary disease has subsided so that once the diagnosis is established treatment must be directed primarily toward the heart

The patient must be kept at absolute bed rest until all signs of active infection within the heart have been absent for one week Before any activity is allowed the temperature pulse rate and blood pressure should be normal The electrocardiogram leukocyte count and sedimentation rate of the red blood cells also must be within normal limits Once the decision is made to allow the patient out of bed activity must be increased gradually as in any other situation in which the heart has suffered an acute insult All laboratory work should be rechecked at the end of one week of activity and if evidence of reactivation of the inflammatory process appears bed rest must be continued for a longer period

If heart failure occurs the usual treatment for cardiac decompensation must be instituted including the use of digitalis oxygen proper fluid balance and a low sodium diet

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CHRONIC VALVULAR DISEASE

A discussion of the management of the patient with chronic valvular disease must be confined to general principles rather than specific suggestions since the complications of valvular heart disease usually bring the patient to the physician rather than the valve lesion per se Since complications such as congestive heart failure arrhythmias and bacterial endocarditis are discussed elsewhere in this book no attempt will be made to include the management of these problems in this discussion

The major consideration in any individual with known valvular disease is to prevent the development of a cardiac neurosis and to keep the patient in a state of mind in which he considers himself to be a useful member of society Certainly he should be informed that he has a cardiac lesion for only by the knowledge of this fact can he help himself to avoid future difficulty The physician must truly practice the art of medicine when imposing necessary restrictions An attitude of reassurance and optimism to the patient are of prime importance In the absence of heart failure it is usually unnecessary to limit normal physical activity Strenuous exercise

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gardening may be advised for recreation In children normal gymnasium classwork should be permitted whenever possible unless extensive heart damage is present Needless to state every case must be individualized depending on the specific problem involved

The patient must be warned that infections of any type should be treated with respect in order to prevent a recurrence of rheumatic fever or the development of bacterial endocarditis The importance of preoperative treatment with penicillin or aureomycin even with such a minor procedure as dental extraction should be emphasized It is wise to caution against excesses of any kind especially with regard to gain in weight and unusual fatigue Great effort must be made by the physician to instruct the patient how to live within his restrictions Certainly with wise counsel and modern therapeutic weapons the patient with chronic valvular disease may expect greater longevity than was thought possible in the years that have passed

The mere presence of a valvular lesion should not be considered a contraindication to pregnancy or to a surgical procedure that may make life more comfortable All too often these patients are denied the benefits of surgery or the happiness of raising children merely because a heart murmur is present

In all patients with valvular disease periodic examinations are desirable in order that the early development of any complication may be noted Careful observation and judicious treatment will aid many patients with organic heart disease to live long and useful lives

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PERICARDITIS

Pericardial disease may occur as an isolated entity as a part of acute heart disease or secondary to a systemic illness It is a not uncommon condition as is shown by the survey of Smith and Willius in which they found postmortem evidence of pericarditis in 4 2 per cent of over 8000 cases at necropsy White states that evidence of pericarditis is found in about 5 per cent of necropsy examinations

Acute Pericarditis Acute pericardial disease occurs most commonly as the result of rheumatic fever and in certain infectious diseases as pneumonia influenza and tuberculosis The pericarditis resulting from acute myocardial infarction and uremia will not be discussed in this section

The treatment of acute pericarditis must of necessity depend on the causative disease If an acute systemic infection is present such as pneumonia or meningitis penicillin streptomycin or one of the sulfonamides must be employed depending on the specific organism involved If rheumatic fever is the cause the usual therapeutic measures for this con[illegible] ustra

ardial sac morphine ¼ grain (15 mg) codeine ½ grain (30 mg) or salicylates 15 grains (1 gm) may be used to control the pain Bed rest must be enforced until all evidence of pericardial involvement has subsided An ice pack over the precordium may aid in keeping the patient comfortable Barnes and Burchill have pointed out that acute nonspecific pericarditis following upper respiratory tract infections may simulate acute myocardial infarction In these patients diagnosis is often difficult and they must be treated with bed rest until the electrocardiogram returns to normal The prognosis in this type of pericarditis is excellent as compared to the outlook in coronary thrombosis

The course of acute pericarditis must be carefully observed for signs of the development of fluid in the pericardial sac The appearance of an effusion need not be cause for alarm unless signs of a rise in venous pressure and fall in arterial pressure occur If these findings which indicate a very high intrapericardial pressure become apparent then tapping of the pericardial sac should be carried out

The best location to try the tap is usually in the fifth intercostal space just inside the outer border of percussion dullness The skin should be thoroughly cleansed and anesthetized with 2 or 3 cc of 0 5 per cent novocain solution The exploring needle should be inserted slowly between the ribs

pointing slightly inward toward the spinal column As the needle enters the pericardial sac a sense of resistance will be noted If the needle moves with the contraction of the heart it should be slightly withdrawn Fluid may then be easily aspirated if it is a serous effusion If this attempt is not successful the needle should be withdrawn and the same procedure repeated in the fourth intercostal space slightly closer to the left sternal border As much fluid as is possible may be removed without ill effect The introduction of a small amount of air 50 to 100 cc into the pericardial sac may prevent the development of adhesions but this is not advisable as a routine procedure The entire operation must be carried out with strict aseptic precautions

It is usually not necessary to tap the pericardial sac more than once but in extreme cases paracentesis may be repeated every 4 [illegible]

[illegible] tion of pericardial fluid

If it is suspected that a purulent fluid is present a large trocar should be used for aspiration It is imperative that drainage be adequate and in most cases incision and drainage is necessary The introduction of penicillin or streptomycin into the pericardial sac each time aspiration is carried out is of definite value when susceptible organisms are the etiologic agent If after two or three injections of an antibiotic no improvement occurs then pericardiostomy must be done Fatalities may result from withholding surgical drainage in a patient who does not improve with conservative management The administration of parenteral antibiotic therapy must be carried out in all cases of purulent pericarditis

Chronic Constrictive Pericarditis The only important form of chronic pericarditis from the therapeutic standpoint is constrictive pericarditis In this condition the heart is encased in a dense covering of adhesions and in some cases deposits of calcium may be present This encasement of the heart prevents adequate diastolic filling and results in a diminished cardiac output and marked elevation of the venous pressure The only way to correct such a condition is to free the heart of this mechanical burden by resection of the pericardium Before operation is attempted adequate preoperative preparation is imperative The patient must follow a low sodium high protein diet All abnormal collections of fluid should be removed from the body by use of ammonium chloride 15 grains (1 gm) four times daily and mercurial diuretics Thoracentesis and paracentesis may be necessary in order to relieve hydrothorax and ascites Digitalis is seldom indicated in constrictive pericarditis unless it be to slow the rate of auricular fibrillation If this arrhythmia is present the risk of surgery is greatly increased

Careful evaluation of hepatic function is desirable preoperatively If extensive liver damage has resulted from prolonged passive congestion the prognosis is much less favorable than in the individual who shows little evidence of impaired hepatic function

Postoperatively the administration of oxygen by mask or tent is imperative Sodium restriction in the diet and in parenterally administered fluids is important The use of mercurial diuretics may be necessary to aid in elimination of recurrent edema Digitalis may be of value following operation to restore compensation to a myocardium that shows signs of failure as a result of the surgical procedure

In some patients dramatic results may appear within several days following operation If however the disease is of long standing as is usually the case 6 months to a year may be necessary before full benefit of the surgical procedure is obtained.

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HEART DISEASE IN PREGNANCY

Prenatal Considerations The management of the pregnant patient with organic heart disease requires keen judgment and careful observation for the 9 month period of the pregnancy and often well into the puerperium There must be co operation between the obstetrician and internist or cardiologist if the optimal results in reducing maternal and infant morbidity and mortality are to be attained

Certain routine precautions must be observed more rigidly in the pregnant cardiac patient than in an otherwise normal pregnant woman *Fatigue must be avoided at all costs*, and long shopping trips or excessive exercise is forbidden Upper respiratory tract infections must be treated with great care and obesity avoided *Anemia must be prevented or corrected with adequate medication*

A thorough understanding of the changes that occur in the circulation during pregnancy is essential for the efficient management of the pregnant patient with heart disease For this reason a brief *résumé* of physiologic principles is included here

Cardiac output, blood volume, and velocity of blood flow increase during pregnancy Many observations indicate that the maximal load is reached early in the eighth month and during this period the work of the heart is increased approximately 50 per cent During the ninth month however, heart failure may appear for the first time, as emphasized by Bunim and Rubricus, so that the last lunar month is not without danger

By far the most common type of cardiac disability found in the pregnant woman is rheumatic heart disease It must be emphasized that the mere presence of a cardiac lesion should not be the cause for alarm It is always cause for careful and frequent observation of the patient Many individuals with cardiac damage go through pregnancy uneventfully and deliver normal babies Certainly the mere presence of organic heart disease should not be considered as cause for therapeutic abortion The most important factor to be evaluated is the functional efficiency of the heart, the history or presence of congestive heart failure must be considered as a signal of impending danger in the pregnant woman If a history of cardiac failure is obtained, it is unlikely that the heart will *stand* the burden that pregnancy demands and interruption is advisable Throughout the prenatal period the patient should be examined every 7 to 14 days Persistent rales at the bases of the lungs dyspnea, and cough herald the onset of congestive failure If these signs appear during the first 6 months, the patient must be put to bed and the cardiac efficiency restored to the best possible state When the patient is in satisfactory condition, interruption of the pregnancy should be carried out by abdominal hysterotomy If the onset of decompensation is delayed beyond 6 months the patient should be confined to bed and managed by the usual methods of treatment for cardiac failure

Bed rest must be enforced until spontaneous labor occurs Delivery is best carried out with the aid of an episiotomy and low forceps *Even if compensation is not restored* it is unwise to add the burden of any operative procedure to the failing heart Hamilton and Thompson point out that the mortality rate in their series was four times greater with abdominal than pelvic delivery Manipulative maneuvers must be avoided unless absolutely indicated from the obstetrical standpoint

The presence of auricular fibrillation, like that of heart failure, must be cause for concern If chronic fibrillation is present, it is wise, when possible, to avoid pregnancy The onset of this arrhythmia during early pregnancy is an indication for abortion During the last trimester, bed rest and digitalis or quinidine, when the heart rate is rapid may succeed in carrying the patient successfully to term

Anesthesia More important than the anesthetic itself is the method of administration Whenever possible, a person trained in anesthesia should be present during the delivery of the child Ether, by the open drop method or, if the closed system is employed with liberal amounts of oxygen is well tolerated by the cardiac patient Nitrous oxide and oxygen should be avoided because of the

danger of asphyxia Spinal anesthesia may be used provided a drop in blood pressure is prevented

Postnatal Consideration It is unusual for the heart to fail for the first time or for failure to recur after delivery If heart failure does appear during the puerperium, one should suspect the presence of a complication such as embolism, atelectasis, or shock It is wise to keep the patient in bed for 2 to 3 weeks following delivery in order to allow the circulatory changes to return more fully to normal Lactation is not harmful to the cardiac patient

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HEART DISEASE IN THE SURGICAL PATIENT

With present advances in anesthesia, chemotherapy, antibiotics, and knowledge of fluid balance, the cardiac patient need not be denied necessary surgical intervention Careful preoperative preparation may convert a poor surgical risk into a satisfactory candidate for the surgeon's scalpel

A careful cardiac history and physical examination are of prime importance in the preoperative evaluation In addition to the usual laboratory procedures, a roentgenographic examination of the chest and an electrocardiogram should be made No effort should be spared to determine the functional efficiency of the heart Studies of the circulation time, vital capacity, and venous pressure should be carried out when necessary

The mere presence of organic heart disease need not be cause for alarm Any patient who is capable of carrying on his normal daily activities without distress will tolerate an operation with little difficulty All too often, individuals are denied the comfort or increased life expectancy which well chosen operations may offer merely because of the existence of a heart murmur or evidence of cardiac enlargement A carefully performed operation adds no more load to the circulation than the daily activities of the patient However, in many patients with heart disease, certain factors exist which greatly increase the risk of surgery, and in these individuals careful judgment and expert treatment are imperative if the patient is to survive

Congestive heart failure should be relieved before any operative procedure is attempted unless an extreme emergency exists The use of rest, digitalis, diuretics, and dietary restriction of sodium will hasten the restoration of compensation It is wise to have the patient [illegible]

After full digitalization, it is wise to continue maintenance dosage of digitalis and this drug may have to be administered parenterally during the first few days following operation Oral food and fluid intake should be encouraged as soon as possible and care must be taken not to overload the circulation with excessive amounts of intravenous fluids Usually 2500 cc of fluid will adequately satisfy the need for water and if this amount is administered slowly, no grave results will ensue The use of oxygen postoperatively is of great benefit to the failing heart and its routine administration for the first 24 hours postoperatively may be of definite value Deep breathing and frequent moving must be encouraged to prevent pulmonary complications and early ambulation is advisable when possible

A major problem requiring careful judgment is the patient with coronary artery disease Certainly no person with evidence of a recent myocardial infarction should be op-

erated on until a minimal period of 8 weeks has elapsed Operation should be postponed even longer whenever feasible The presence of angina pectoris is an ominous sign and when this condition exists elective surgery should be avoided Unfortunately many older individuals with definite coronary atherosclerosis require operations and in these patients surgery must be carried out despite the increased risk Vasodilators such as aminophylline 3¾ grains (0 25 gm) administered intravenously or 7½ grains (0 5 gm) intramuscularly may be of slight value in increasing the coronary circulation preoperatively and postoperatively More important however than drug treatment is careful administration of a well chosen anesthetic and the avoidance of drops in blood pressure and shocklike states Prostatic operations usually because of the age group in which they are necessary may precipitate coronary thrombosis and in these patients sudden drops of blood pressure may prove fatal (Master Dack and Jaffe Kretschmer and Butler)

The presence of auricular fibrillation increases the risk of surgery especially in pa

in non fibrillators to 22 2 per cent in patients with this arrhythmia in which rheumatic heart disease was the etiologic factor Sprague also emphasizes that auricular fibrillation in the arteriosclerotic individual is not nearly as grave a sign as in the rheumatic

the drug of choice If quinidine is used it should be administered in a dose of 3 grains (0 2 gm) four times daily for the first day and if this dose does not control the arrhythmia the drug may be increased to 0.2 gm every 2 to 3 hours If any symptoms of idiosyncrasy become apparent quinidine should be *discontinued In patients suffering from* hyperthyroidism the presence of auricular fibrillation need not be cause for alarm provided adequate preoperative preparation of the metabolic state was adequate More often than not the heart condition will actually be improved by subtotal thyroidectomy The use of antithyroid drugs such as 6 propyl thioura*cil may supplant the need of surgery* in extreme cases in which the risk of operation is high

Chronic valvular disease does not *greatly* increase the surgical risk if heart failure or an arrhythmia is not present It is exceedingly important however that all such patients be adequately treated with penicillin or aureomycin before and after surgery to prevent the development of a valvular infection Subacute bacterial endocarditis may result from as minor a procedure as a dental extraction and antibiotic or chemotherapy greatly reduces *the danger of this complication*

In addition to the above problems certain general considerations should be mentioned Obesity increases the risk of postoperative complications in any patient and especially *in cardiac patients Whenever possible ade*quate weight reduction should be enforced before any elective surgical procedure is attempted

Infection should be controlled at all times with properly chosen drugs and whenever possible the causative organism should be accurately identified in order to determine the most effective agent for its eradication

Postoperative dilatation of the stomach or gaseous distention of the bowel may hamper normal respiratory effort and these complications must be treated as soon as their appearance is observed

The choice of anesthetic for the cardiac patient must be made with care and when poss ble the aid of a trained anesthetist should be sought Adequate sedation preoperatively is of great value in allaying the anxiety of the patient and in facilitating the induction of the general anesthetic Cardiac patients *tolerate ether well Sodium pento-*

heart failure spinal anesthesia may be used provided all precautions to prevent drops in blood pressure are observed Cyclopropane must be administered only by one thoroughly familiar with its use This agent may produce abnormalities of cardiac rhythm and for this reason its value is limited During the administration of any anesthetic, *anoxia and* violent muscular contractions must be avoided

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CARDIAC TRAUMA

The diagnosis of injury to the heart is

to any part of the body, provided it is of sufficient violence, and its force is transmissible to the heart," emphasizes the necessity of careful cardiac examination in any injured person It is possible for a variety of injuries to occur such as penetrating wounds, rupture of the valves or septum, rents in the endocardium and hematoma formation or contusion of the muscular wall

Once the diagnosis of a cardiac injury is made, the patient should be kept at absolute bed rest and if signs of cardiac tamponade appear, immediate surgical intervention should be attempted Morphine may be used freely and the usual measures to combat shock should be instituted If abnormal rhythm is present, quinidine, 3 grams (0 2 gm), four times daily may prevent the development of ventricular fibrillation

In contusions of the heart muscle absolute bed rest should be maintained for a minimum period of 6 weeks An anginal type of pain may be present resulting from injury to the coronary arteries Frequent electrocardiograms should be made in order to follow carefully the progress of the cardiac lesion When the patient is allowed out of bed, the return to activity must be slow and graduated

If evidence of pericardial effusion becomes apparent, it is wise to remove the pericardial fluid in order to prevent further embarrassment of the already damaged heart The development of cardiac failure requires the usual treatment, as described elsewhere in this book

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CARDIAC DECOMPENSATION

Normally the work of the heart may be increased within wide limits without the production of undue symptoms During severe muscular exercise the cardiac output may increase as much as 900 per cent of the resting value In sedentary individuals this range of increase is much less than in those accustomed to strenuous physical work The range of normal response to exercise varies considerably in different persons, it tends to decrease gradually as the individual grows older Broadly speaking, heart failure may be said to occur when there is curtailment of the remarkably broad power of accommodation of the heart to the ever varying demands of the organism Evidence of heart failure is manifested by certain symptoms shortness of breath on exertion and even at rest, easy fatigue on effort, precordial discomfort, and certain signs, e g, breathlessness, orthopnea, dyspnea, cyanosis, pulmonary rales, pleural effusion, distention of veins and increased venous pressure, congestion of the liver, ascites, and edema of the lower extremities

We shall confine our remarks to the subject of backward failure, that is, heart failure involving the left heart, the right heart, and a combination of both In left heart failure, the manifestations are observed particularly [illegible]

liver, increased venous pressure, ascites, and edema of the lower extremities The symp-

toms and signs of heart failure may be simulated by those of other conditions especially pulmonary disease anemia bronchogenic and peritoneal carcinoma cirrhosis of the liver avitaminosis and other acute or chronic ailments

Factors Inducing Heart Failure Before discussing the treatment of heart failure in detail it is well to mention the factors responsible for the induction of the heart failure since an appreciation of these factors will result in more intelligent and adequate therapy (1) Increased work Under this heading may be placed thyrotoxicosis arrhythmias with rapid ventricular rate valvular lesions hypertension arteriovenous fistula and pregnancy (2) Impaired nutrition of the heart Under this category may be mentioned anemias of various types coronary disease and malnutrition (3) Pulmonary heart disease This includes pulmonary arteriosclerosis pulmonary fibrosis pulmonary emphysema and the end results of multiple pulmonary emboli (4) Inflammatory heart disease The most common types are rheumatic myocarditis associated with subacute bacterial endocarditis diphtheritic idiopathic type of interstitial myocarditis and virus infections (5) Degenerative This includes coronary artery disease with myocardial fibrosis fatty degeneration and amyloid disease (6) Avitaminosis Beriberi is the most important type (7) Extrinsic This includes pericardial effusion and pericardial adhesions (8) Various combinations of the above

Methods of Treatment The treatment of heart failure will be discussed under the following headings (1) rest of the heart (2) treatment of cardiac edema (3) treatment of acute left heart failure (4) surgical measures and (5) other methods of therapy (chemotherapy treatment for impaired nutrition altered metabolic states electrolyte changes and climate)

Rest of the Heart Rest of the heart may be divided into two categories (1) bed rest and (2) decrease of cardiac work while the patient is resting in bed

BED REST The importance of bed rest in the treatment of heart failure cannot be overemphasized Bed rest not only reduces the work of the heart to a minimum but decreases the metabolic demands of the tissues for blood The value of bed rest is not as equally applicable to left as to right heart failure In left heart failure the period of bed rest in some patients may be curtailed to about 1 or 2 days thereafter the patient frequently does better by sitting in a chair which causes a considerable amount of fluid to gravitate to the lower portions of the body thus diminishing the strain on the heart In the presence of right heart failure bed rest may be prolonged to 2 or 3 weeks depending on the individual case Recent knowledge relating to the abuse of bed rest is important in this connection This is particularly applicable to patients with heart disease especially in the older age groups Some of the deleterious effects of bed rest are tendency to develop hypostatic congestion of the lungs and pneumonia phlebothrombosis with pulmonary infarction and occasionally arterial thrombosis Patients with phlebothrombosis and patients above the age of 50 should be encouraged to exercise their arms and legs and to move around in bed and be allowed out of bed as soon as their condition permits The use of anticoagulants as a prophylactic measure against development of vascular occlusion in such patients and particularly those with auricular fibrillation is gaining more popularity

LOW CALORIE DIET A low calorie diet 800 to 1000 calories reduces the work of the heart by reduction of the metabolic rate which may drop to −20 or −30 Obesity is an additional indication for weight reduction Obesity involves an added strain on metabol

function Frequently a loss of weight down to the optimal range may not only improve the exercise powers of the patient but may postpone for years the onset of heart failure

THIOURACIL Thiouracil acts by reducing the basal metabolic rate its use depending on physiologic principles similar to those mentioned under thyroidectomy Propyl thiouracil which is less toxic than thiouracil has been tried in occasional patients with heart failure unassociated with thyroid toxicity as well as those with thyrotoxicosis its

use however has not gained much popularity

Treatment of Rapid Rate The occurrence of an arrhythmia with a rapid ventricular rate results in myocardial exhaustion owing to the abbreviation of the diastolic rest period of the heart A rapid ventricular rate if sufficiently prolonged may induce heart failure even in a normal heart this occurs with greater ease in an already damaged heart A rapid ventricular rate associated with auricular flutter or auricular fibrillation responds to digitalis Auricular paroxysmal tachycardia may be abolished by carotid sinus pressure by prostigmine plus carotid sinus pressure by digitalization or by the administration of quinidine Nodal tachycardia yields to similar therapeutic measures Ventricular paroxysmal tachycardia can usually be abolished by quinidine

Treatment of Edema The underlying principles of the treatment of edema of cardiac origin consist of (1) the administration of the mercurial diuretics (2) digitalization (3) restriction of sodium with fluid intake limited to 1200 to 2500 cc per day (4) mechanical removal of the effusion

The extracellular fluid may increase by 50 per cent before actual edema becomes evident In this stage of "preclinical decompensation" as emphasized by Christian many years ago there may be symptoms of breathlessness fatigue and slight swelling of the ankles toward evening This stage may last for many years before manifest heart failure is evident Such patients are markedly improved by the regimen outlined for the treatment of heart failure

Diuretics The use of the mercurial diuretics is probably the most important single method employed in the treatment of heart failure *These act by preventing the reabsorption* of sodium by the renal tubules considerable amounts of sodium are therefore eliminated in the urine and large amounts of water are carried off with this electrolyte This diuretic may be given intravenously intramuscularly subcutaneously rectally or by mouth* It is about equally efficacious when it is given intravenously or intramuscularly The oral administration of mercurial diuretics has the following disadvantages (1) it is less effective than the intramuscular or intravenous route (2) it often produces gastric irritation (3) occasionally it tends to produce toxic renal effects (4) it occasionally produces an ulcerative stomatitis (this rarely occurs with the parenteral methods) Rectal administration of mercurial diuretics while efficacious is not desirable because it frequently produces a proctitis

Relatively few contraindications to the administration of the mercurial diuretics exist In the presence of heart failure they may be given even when a cloud of albumin is present in the urine and with mild to moderate degrees of azotemia They have occasionally

chief contraindications to their use are in acute glomerulonephritis and marked grades of azotemia which are considered to be the result of primary renal disease and not the result of congestive failure

The patient should be weighed on admission and daily during the administration of the diuretic The frequency of its administration in the initial stages of congestive failure is as follows an initial dose of 0 5 to 1 cc may be given intramuscularly and this may be repeated daily until a considerable amount of fluid is removed Thereafter the dose may be given every other day or every third day until that stage is reached when most of the extracellular fluid has been removed The patient is then put on a maintenance dose which may be given every one or 2 weeks as indicated

The favorable effects of this drug consist in a marked diuresis which may reach as much as 6000 to 7000 cc following a single injection A patient may lose as much as 10 lbs of body weight with a single dose with no untoward symptoms and with considerable improvement however relatively little or moderate diuresis may be accompanied by asthenia The objective in the administration of the mercurials is to reduce the body weight to a level at which the optimal volume of extracellular fluid remains This has

* [illegible]

been called by Gold and others the "dry weight" When this point is reached the mercurial diuretics usually have little diuretic effect

Untoward effects following the administration of mercurial diuretics are not infrequently encountered Sudden death has been reported following intravenous administration it has not been observed following intramuscular administration The mechanism of death in these patients has not been definitely ascertained It usually occurs quite *suddenly immediately following the injection* and has been attributed to an allergic factor or a toxic effect of the mercury on the heart The intramuscular route is the most popular method of administration because it is relatively safe has no painful effects and can be administered by a nurse Some care must be exercised in the use of the mercurials in older patients and those with asthenia they should be used with caution in hot weather Such patients may experience weakness apathy leg cramps a shock like state and even death These episodes may be observed as a result of loss of electro*lytes especially chlorides and sodium* and occasionally calcium Peters has recently observed instances where the plasma sodium was low prior to the administration of the mercurial diuretics Following the use of the mercurial the plasma sodium may drop to a dangerously low level Such untoward effects may be prevented by the administration of smaller doses of the mercurials (for example 0 5 cc) by the administration of salt prior to and immediately following the

poor diet. The estimation of serum electrolytes of patients under prolonged treatment with mercurial diuretics should be a more *common* practice

Instances of coronary occlusion have at times been observed following the use of the *mercurials* Whether or not this is the result of increase in the blood viscosity due to excessive dehydration has not been established *Occasionally in a previously digi*talized patient the mercurial diuretics may be followed by the production of numerous extrasystoles which are believed to be the result of redigitalization due to the action of this glucoside contained in the reabsorbed extracellular fluid

Even though this drug has been given for long periods of time up to 2 and 3 years and at frequent intervals there is little evidence that it itself produces kidney pathology However occasional *instances of* renal shutdown with intractable anuria have been observed

Not *infrequently patients who have re*ceived the mercurial diuretics with good response over a period of months or years reach a period when they no longer respond to this diuretic The treatment of such "mercurial fast" patients involves a rather serious problem One should differentiate such patients from those where oliguria is present due to mechanical factors e g in the presence of marked ascites and where the blood pressure has fallen to shock like levels Following the removal of ascitic fluid and restoration of the blood pressure to a more normal level a diuresis may again be observed If without obvious cause, several doses have been given and no diuretic effect is obtained it is usually dangerous to ad*minister the drug further because its reten*tion in the body may be toxic In the

administration of 10 per cent glucose If these methods fail peritoneal *lavage has* been advised This is a rather dangerous procedure and should be used only as a last resort

Other Diuretics Other diuretics may be used alone or as an adjuvant to therapy with the mercurial diuretics Ammonium chloride 3 to 6 gm per day may be used as adjuvant to the mercurial diuretics but it is usually not necessary The xanthine drugs are occasionally used for their diuretic effect However by themselves they rarely suffice in the treatment of congestive heart failure The following may be given theobromine 0 6 gm three to five times a day theobromine sodium acetate 0 5 gm three times a day theophylline ethylene diamine 0 5 gm three to five times a day Urea in a dose of 20 gm may be administered two to five times a day Because it is difficult to take by itself it is usually given with fruit juices iced fluids or syrup

DIETARY REGIMEN *Salt and Water Intake* A low calorie, salt poor diet is preferred during the initial stage of heart failure For this purpose the Karrel diet may be used This consists of 1000 cc of milk per day which contains 1 gm of salt The patient is placed on this diet for several days or a week and after a satisfactory diuresis has resulted this may be increased in caloric content and type of food The fluids may then be increased to 2000 to 3000 cc per day and the salt intake to 2 gm The importance of a salt poor diet cannot be overemphasized The normal daily diet contains about 10 gm of salt Patients with heart failure can eliminate only about 2 to 3 gm per day The usual salt poor diets in the hospital or at home contain 5 or 6 gm of salt The salt which cannot be eliminated is retained in the body with the resultant production of edema The best way to keep a patient on a dietary regimen of about 0 5 to 1 gm of salt per day is to peruse meticulously each item of the diet and make sure that it is salt free Even salt free bread may be obtained Salt substitutes may be used to make the diet more palatable For this purpose Neocurtasal and Cosalt are recommended

REMOVAL OF EFFUSIONS Removal of pleural effusions and ascitic fluid may indirectly help the heart and may enable the diuretics and digitalis to act more efficiently Pericardial effusions resulting from congestive failure are rarely large enough to require paracentesis when other methods have failed Southey tubes may be used in the occasional case where it is necessary to drain off the edematous fluid from the lower extremities

Digitalis in Heart Failure PREPARATION AND DOSAGE Many preparations of digitalis drugs are available for the treatment of heart failure The type of preparation depends on individual preference and the mode of administration, whether the drug is given by mouth, intravenously, or intramuscularly The most popular method of administration is by mouth and the following preparations are commonly used the powdered leaf, digitoxin, digoxin digilanid, lanatosid C, and cedilanid The following table lists the drugs the amount required for full digitalizing dose, and recommended daily maintenance dose

TABLE I

Drug	*Digitalis Dose Full Digitalization*	*Daily Maintenance Dose*
Digitalis leaf	15 cat units (22½ grams)	½ to 1 cat unit
Dig lanid	15 cat units (5 0 mg)	¼ mg
Digitoxin	1 2 to 3 6 mg	0 05 to 0 2 mg
Digoxin	2 to 5 mg	0 25 to 0 75 mg
Lanatosid C	7 5 mg	0 5 to 1 2 mg
Cedilanid	5 to 10 mg	0 5 to 1 5 mg

The initial digitalizing dose is that recommended for a patient weighing 150 lbs (about 70 kg) However, the dose required for full digitalization in different patients varies considerably, sometimes twice or more of the recommended dose is required Although the recommended digitalizing dose is sometimes administered at one time, it is best to give half of this dose initially and the remaining 50 per cent in two portions at 12 hour intervals Toxic effects rarely occur with the lower digitalizing dose mentioned, they not infrequently occur with higher doses The following patients develop toxic effects on the smaller dose and should be given digitalis with care patients with aortic stenosis, those manifesting a severe grade of myocardial damage, those with overactive vagal tone and patients in the older age group

The maintenance dose of the digitalis drugs also varies considerably in different patients and at different times in the same patient It is suggested that following digitalization the average dose for maintenance be given to the patient The patient should not be kept on this dose indefinitely but should be frequently checked and the dose increased or decreased depending on the patient's need and response

Recently the trend has been to administer the pure glucosides, digitoxin digoxin cedilanid, or lanatosid C rather than the powdered leaf The advantages in doing this are the smaller dosage, the greater accuracy in standardizing the drug and the absence of local irritating effects on the gastro intestinal tract However, the action of these purified preparations is not always identical with that of the powdered leaf They vary in the degree of muscular and vagal effects and the dosages even in patients with auricular fibrillation and are difficult to compare with those of the powdered leaf which has been

so extensively used for many years For example, following the recommended dose of the purified preparation, the ventricular rate in auricular fibrillation may drop to 70 or 80 per minute When this point is attained, exertion or excitement frequently elevates the rate far above that which would be attained with the patient on the powdered leaf Additional doses of the purified preparation are required to prevent this excessive response following exercise and emotion The following point may be made the minimal dose of digitalis that will decrease the ventricular rate to 70 per minute at rest is not necessarily the optimal digitalizing dose

In the past few years, digitoxin has largely replaced the powdered leaf for routine digitalization However, the frequent development of toxic effects in patients under treatment with digitoxin has led to the re-evaluation of the use of this drug in the treatment of heart failure by DeGraff, Batterman and Rose, and others They found that digitoxin has a greater cumulative effect than other digitalis preparations and that the maintenance dose, 0 2 mg , recommended by Gold, often results in toxicity after about 4 to 6 weeks It is their opinion that digitoxin offers no advantage over the digitalis leaf and because of the possibility of severe and prolonged toxicity, digitoxin is not the glucoside of choice

PARENTERAL ADMINISTRATION The intravenous preparations of digitalis drugs and their full digitalizing doses are strophanthin (1/60 gram), digitoxin (1 2 mg), cedilanid (1 6 mg), and digalen, 3 to 5 cat units The following preparations may be given intramuscularly ouabain, 1/240 grain, or digalen, 3 to 5 cat units

The intravenous administration of digitalis drugs is indicated in those patients in whom it is mandatory to obtain a rapid effect and where administration by mouth is considered to be too slow and undependable, for example, patients with severe grades of advanced heart failure following the occurrence of rapid auricular fibrillation or flutter In some of these cases the intravenous administration results in almost immediate and dramatic effects An effect from strophanthin may be obtained as early as 5 minutes after its administration It is important to remember that the intravenous route carries with it added danger of toxicity This route should not be used in a patient who has been receiving digitalis for the past 2 weeks It is safer to administer half of the intravenous digitalizing dose and wait one half to 1 hour in order to note the effect of the initial dose before any of the remainder is given Often a sufficient degree of improvement is obtained with the initial dose to warrant giving additional doses by safer routes (intramuscularly or by mouth) While strophanthin acts rapidly, it has the additional advantage of being dissipated rapidly so that after its full effect is obtained, digitalization by mouth may be started

The intramuscular route is indicated in those patients where the need for haste is not as urgent as that mentioned above, but where it is desired that absorption be relatively rapid and dependable

TOLERANCE The tolerance for digitalis varies considerably with the age of the patient, the type and severity of the heart condition, and the absence or presence of heart failure In general, it may be said that older patients and those with greatly damaged hearts have a decreased tolerance to digitalis and manifest a narrow range between the therapeutic and toxic effects In such patients, toxic effects may occur long before [illegible]

damage Patients with partial A-V block and those with aortic stenosis are apparently more susceptible to the development of increasing degrees of heart block on relatively small doses of the drug

TOXICITY The most important symptoms of the untoward effects of digitalis are malaise, headache, anorexia, nausea, vomiting diarrhea, and occasionally psychoses and ocular symptoms The initial symptoms mentioned, malaise, headache, and anorexia, may [illegible]

is well to remember that nausea and vomiting may be present as the result of the local irritating effect of this drug on the gastric mucous membrane when the powdered leaf has been given This is less true when the purified preparations are administered It

should be emphasized that vomiting is not invariably present with digitalis toxicity, extremely dangerous evidences of its action may be present without either nausea or vomiting This is especially prone to occur in those with advanced grades of heart disease and in senile patients Instead, these patients often present marked weakness and asthenia with clear cut evidence of toxicity in the form of dangerous cardiac irregularities These cardiac manifestations are often more dependable signs of digitalis toxicity than vomiting

Psychoses are observed as an occasional toxic effect In those patients where we have observed this to be present, it was apparently the result of the concomitant cerebral circulatory disturbance rather than the direct effect of the drug

Ocular symptoms in the form of spots before the eyes and various colors (green, blue, and yellow) may be observed This condition is usually temporary and disappears with the elimination of the drug The eyegrounds show nothing abnormal These effects are believed to result from the direct toxic effects of the drug on the primary optic centers in the brain

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is indicated when (1) the heart rate drops to 60 or below (2) a formerly regular pulse becomes irregular, (3) a bigeminal pulse is present, (4) the cardiac rate, previously between 80 and 100 suddenly becomes rapid and irregular, 140 to 180 per minute

Although the clinical evidence of toxicity is important the most accurate method of confirming this suspicion is by means of the electrocardiograph As initial evidence of its action there is observed depression of the ST segment and inversion of the T wave Digitalis commonly alters the T wave and ST segment in a definite and characteristic manner The P R interval, or A V conduction time, becomes prolonged and heart block of various grades may result In some electrocardiograms several of these evidences of the drug s action may be observed in one tracing Most of these electrocardiographic alterations may occur within the therapeutic range of digitalis action The presence of the following however are unequivocal signs of toxicity high grade A V heart block, going into complete block, A V dissociation with ventricular escape, numerous ventricular extrasystoles, coupled rhythm, auricular tachycardia with A V heart block and ventricular tachycardia The treatment of these ectopic rhythms consists of cessation of further digitalis medication Quinidine may be of help in abolishing the ventricular extrasystoles, coupled rhythm, and ventricular tachycardia

In summarizing it may be stated that in the administration of digitalis, three points to be noted are (1) the maximal therapeutic effects, (2) the beginning toxic effect, and (3) the definite toxic action The boundary between the maximal therapeutic and the beginning toxic effect is often not clear cut It is difficult to determine this point clearly in patients with normal sinus rhythm The maximal therapeutic effect of its action is most clearly marked in patients with auricular fibrillation There it may be said to be present when the cardiac rate has fallen to 70 with an elimination of the pulse deficit This point does not necessarily coincide with the maximal possible degree of improvement in the patient Edema may still be present and require the use of the mercurial diuretics for its abolition

Treatment of Acute Left Heart Failure In general the principles of treatment in acute left heart failure consist of (1) treatment of the cause namely the underlying heart condition such as coronary artery disease, aortic or mitral valvular disease, or hypertension (2) abolition of certain reflexes and treatment of rapid ectopic rhythm which may precipitate the attack, and (3) decrease of the circulating blood volume so that the damaged heart may be able to perform its functions with a lesser degree of strain

[illegible]

... ation of morphine sulfate, 10 to 15 mg given alone or accompanied by atropine, $\frac{1}{150}$ to $\frac{1}{75}$ grain The morphine sulfate may be given subcutaneously, intramuscularly, or at times (during a shock like state) intravenously The earlier it is given following the inception of an attack, the better will be the *therapeutic*

result In many patients administration of this drug alone will suffice to abort the attack in about 10 or 15 minutes In older individuals, who are sensitive to the effects of morphine, the respirations may drop to 10 or less per minute In such patients, it is well to administer a respiratory stimulant with the morphine, as for example, caffeine and coramine

Caffeine with sodium benzoate, 0 5 gm, may be given initially and repeated every 2 to 3 hours for about three doses This acts as a respiratory and cardiac stimulant Coramine, 1 cc, may be repeated two or three times over a period of 2 or 3 hours Aminophylline, 0 3 gm, may be given slowly by the intravenous route repeated in about half an hour The beneficial effects of this drug depend on its respiratory stimulating effect and possibly its coronary dilator action

Digitalization may be accomplished rapidly by the administration of strophanthin 1/100 to 1/50 grain or 0 8 to 1 6 mg of cedilanid intravenously if the patient has not been previously digitalized If less haste is required, digalen may be given intramuscularly in a dose of 3 to 5 cat units Generally digitaliza*tion is of less efficacy than the other pro*cedures mentioned for this treatment of the acute attack

Oxygen may be given by nasal catheter, oxygen mask, tent, and at times under posi*tive pressure The administration of oxygen* is important in left heart failure because the heart suffers five times as much from oxygen lack as does skeletal muscle The maintenance of a maximal degree of oxygenation is important for the optimal function of the *heart, particularly at a time when the pul*monary vascular field available for oxygenation is diminished

In a plethoric individual, venesection, 250 to 500 cc, is of aid in rapidly reducing the strain on the left heart This should not be done in an asthenic individual or where the patient experienced frequent attacks of left heart failure, owing to the slowness with which regeneration takes place in such individuals, resulting in anemia A bloodless venesection may be accomplished by the application of tourniquets to all four extremities These may be kept on for 10 or 15 minutes, released in one and kept on three extremities at a time This regimen *is of as* much help in reducing the circulating blood volume as a venesection

The administration of 50 per cent glucose or sucrose has been recommended for the treatment of pulmonary edema, based on their osmotic effects However, we believe that this is a dangerous method of therapy because, by a shift of fluid from the tissues into the blood, the circulating blood volume is increased, this adds to the strain of the already overstrained heart We have seen the intravenous injection of these hypertonic solutions precipitate attacks of left heart failure

Following the attack of left heart failure, the patient should be kept at rest in bed for 1 or 2 days Frequently he feels quite well the morning following the attack and is able to go about his duties After an attack of pulmonary edema, these patients frequently develop a mild grade of bronchopneumonia which usually yields to antibiotics and chemotherapy (penicillin and/or combined sulfonamides)

Prophylactic Measures in Patients Subject to Attacks of Left Heart Failure In patients subject to attacks of left heart failure, *the following measures are helpful in* preventing recurrent attacks (1) a period of bed rest may be of aid in resting the heart by keeping the cardiac output at a minimum (2) restriction of sodium intake to about 0 06 *to* 0 120 *gm per day and restriction of fluids* to about 1200 to 1500 cc per day, (3) digitalization, (4) diuretics in the form of the mercurials one injection (2 cc of mercuhydrin) to be given every week or two, or more frequently, with or without ammonium *chloride, 2 or 3 gm per day,* (5) a light supper with little fluid before bedtime, (6) occasionally these patients are helped by sleeping with the head of the bed propped up about 9 inches from the floor, (7) aminophylline, 0 2 gm, t i d by mouth and/or 0 67 gm administered rectally at bedtime, (8) sedatives preferably the barbiturates, (9) prevention of abdominal distention by careful regulation of the bowels (10) a dietary *regimen to reduce the weight in obese pa*tients

Surgical Treatment in Heart Failure Various surgical procedures have been suggested for the treatment of congestive heart failure These consist essentially of an at

tempt to relieve the strain on the heart by various procedures

Valvulotomies and valvuloplasties have been performed in the presence of mitral stenosis These operations however involve considerable risk and the patients who have been observed following the operations show equivocal improvement Another type of operation has been devised to diminish the strain on the large left auricle One branch of the pulmonary vein has been anastomosed to the vena azygos This results in a short *circuiting of some of the blood from the left* auricle to the systemic venous circulation It results in effect in a recirculation of blood and although it may partially reduce the strain on the left auricle it is doubtful if this operation is the answer to the problem

LEFT HEART FAILURE *Cossio has cut the* tricuspid valve in patients with left heart failure By producing tricuspid regurgitation he has hoped to transfer the strain from the greater to the lesser circulation he has reported several patients who showed marked *temporary improvement following this procedure* However this operation produces an additional heart lesion In addition experience with patients who manifest tricuspid regurgitation indicates this to be a serious lesion itself and such patients generally have a poor prognosis

ADHERENT PERICARDIUM AND CONSTRICTIVE PERICARDITIS Adherent pericardium and constrictive pericarditis may result in heart failure (failure of diastolic filling) Removal of the adhesions around the body of the heart and inferior vena cava has in some cases resulted in cure of the heart failure

THYROIDECTOMY Some years ago Blumgart and his co workers popularized the operation *of total thyroidectomy for the treatment of*

metabolic demand of the tissues decreases the work of the heart Unfortunately this op*eration resulted in the production of cardiac* changes associated with the surgical myxedema as well as accompanying mental changes This procedure except for isolated cases has been generally abandoned

HYPERTENSION Hypertension either alone *or combined with coronary arteriosclerosis* is the most frequent cause of heart failure Hypertension tends to induce left heart failure or right heart failure and frequently a

TABLE II

MODIFIED KARELL DIET OF BANNICK AND SMITH COMPOSITION OF DIETS

Diet	*Carbohydrate*	*Protein*	*Fat*	*Water*	*Calcium*	*Magnesium*	*Potassium*	*Sodium*	*Phosphorus*	*Chlorine*	*Sulfur*	*Iron*
Karell	40	24	32	696	0 96	0 096	1 144	0 408	0 744	0 848	0 272	0 0019
Modified Karell	53	26	40	465	0 40	0 073	0 866	0 583	0 550	0 852	0 368	0 010

Breakfast

Bread (toast)	10 gm
Ten per cent fruit (orange)	100 gm
Sugar	5 gm
Egg	1

Dinner

Bread	10 gm
Cream Soup	150 gm
Butter	5 gm

Supper

Bread	10 gm
Milk	200 gm.
Butter	10 gm.
Egg	1

combination of both right and left heart failure Unfortunately there is as yet no dependable method of treating patients with hypertension so that permanent improvement may be obtained Treatment by potassium thiocyanate vasodilators and sedatives is only partially efficacious and does not have a permanent beneficial effect on the hypertension The use of the salt poor diet the rice diet and the Smithwick operation is of temporary aid in reducing the blood pressure In some few cases the Smithwick operation by reducing the blood pressure has been singularly successful in preventing attacks of heart failure

Other Methods of Therapy IMPAIRED NUTRITION Poor nutritional states may aggravate and at times precipitate heart failure *Their correction is obtained by an adequate* diet, treatment for anemia vitamins and adequate protein intake by the administration of blood and plasma

CHEMOTHERAPY AND ANTIBIOTICS Inflammatory states may also aggravate and at times precipitate heart failure These may be treated by chemotherapy penicillin sulfonamides and aureomycin Diphtheritic infection should be treated with antitoxin Unfortunately there is as yet no adequate therapy for active rheumatic carditis The *sulfonamides and penicillin are apparently* of benefit as prophylactic measures in cardiac patients

TREATMENT OF METABOLIC DISORDERS The adequate treatment of diabetes, particularly the state of coma during the presence of acidosis is of paramount importance since this condition has deleterious effects on the heart Similar therapy should be directed for other types of altered metabolic states such as hyperthyroidism and hypothyroidism hyperparathyroidism and hypoparathyroidism Addison s disease pheochromocytoma gout and other metabolic disorders

ELECTROLYTE CHANGES Alterations in the [illegible] observed in a variety of con

disease and in various metabolic disorders The effects of a low serum sodium have already been discussed Hypocalcemia increases the irritability of the heart muscle A low serum potassium results in a disturbance of function of the already disturbed heart We have observed patients with heart failure who manifested little response to the usual methods of therapy, in whom correction of the electrolyte picture resulted in marked improvement

CLIMATE Patients who have or are prone to develop congestive heart failure do better in a slightly warm or cool environment They do not do well in hot weather The mortality of patients with congestive heart failure is considerable during hot spells This is probably the result of increase in cardiac output loss of electrolytes and excessive thirst with difficult elimination of water The use of air conditioning in hot weather is of considerable benefit to such patients

SAMUEL BELLET

TABLE III

SAMPLE DIET CONTAINING 2000 CALORIES AND 1 0 GM SODIUM CHLORIDE

	Food (gm)	Protein (gm)	NaCl (mg)	Calories
Breakfast				
Bread	40	3 7	30	104
Butter	12	0 1	2	87
Jelly	15		5	35
Cream	40	0 9	31	153
Sugar	15			60
Canned apricots	50	0 5	49	37
Cream of wheat	120	1 3	2	44
Egg (boiled)	50	6 6	179	80
Dinner				
Bread	40	3 7	30	104
Butter	12	0 1	2	87
Jelly	15		5	35
Steak (sirloin)	90	19 9	213	105
Rice	20	1 6	13	71
Butter	15	0 2	3	111
Fresh string beans	75	1 8	35	32
Butter	4			29
Apple raw (sauce)	95	0 4	27	60
Sugar	10			40
Whipped cream	25	0 6	19	96
Supper				
Bread	40	3 7	30	104
Butter	12	0 1	2	87
Jelly	15		5	35
Roast turkey	60	19 0	203	97
Steamed Irish potato	75	1 5	42	64
Butter	12	0 1	2	8[illegible]
Lettuce	20	0 2	10	3
Fresh tomato	50	0 5	16	12
Pot cheese	25	5 2		28
Olive oil	5			45
Canned cherries	75	0 8	44	67
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TABLE IV

Cardiac Diet Weighed and Approximated *

MEALS	gm		LUNCHES	gm	
Breakfast			*9 A M*		
Milk	100	½ cup	Water	100	½ cup
Cream	66	¼ cup	or crushed ice	100	1 cup
Cereal (cooked)	1?0	⅔ cup			
Sucrose	10	3 teaspoons	*10 A M*		
Glucose	10	6 teaspoons	Orange juice	150	¾ cup
Dextrin maltose	10	0	Lemon juice	5	1 teaspoon
Dinner			Sucrose	10	3 teaspoons
Soup: Cream	132	⅔ cup	Glucose	20	6 teaspoons
Soup: Potato	50	¼ cup			
Soup: Butter	10	2 teaspoons	*3 P M*		
Ice Cream	100	¼ cup	Milk	100	¼ cup
or junket †		⅔ cup	Cream		¼ cup
Milk	100	½ cup	Flavoring		
Water	100	½ cup	Dextrin maltose	12	4 teaspoons
or crushed ice	100	1 cup	Sucrose	5	1 teaspoon
Supper			*4 P M*		
Soup: Cream	66	¼ cup	Water	100	½ cup
Soup: Milk	100	½ cup	or crushed ice	100	1 cup
Soup: Spinach ‡	50	¼ cup			
Butter	10	2 teaspoons	*7 P M*		
Custard: Egg	50	1 egg	Milk	150	¾ cup
Custard: Milk	100	½ cup	Dextrin maltose	10	3 teaspoons
Custard: Lactose	10	3 teaspoons	or candy		1 stick
Custard: Glucose	10	3 teaspoons			

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DISEASES OF THE BLOOD VESSELS

HYPERTENSIVE VASCULAR DISEASE

General Considerations as Related to Treatment Treatment of patients with hy pertensive vascular disease is based on a definitive diagnosis and classification of the kind of malady from which the patient suf fers Arterial hypertension like fever or leukocytosis is of multiple origin No dis *cussion of its treatment is possible which* does not presuppose an estimate of the na ture extent and rate of progress of the dis ease

The term "hypertensive vascular disease has value because it is broad and inclusive It means a state in which arterial tension is increased over long periods of time and one which is usually associated with premature damage to blood vessels and to the tissues and organs they supply It has no etiologic and often little physiologic connotation It includes a *most common lethal disease of* adult life namely essential hypertension The cause of this disease is unknown The term also includes a variety of secondary sometimes transitory hypertensive states the origin and nature of which are either known or suspected on adequate clinical and functional grounds While this review of treatment is concerned more particularly with "essential hypertension it is also neces sary to review some of the other types of hypertensive disease which simulate essen tial hypertension

Essential hypertension is characterized by persistent elevation of systolic and diastolic arterial pressures In its early stages which begin probably in the 20s and 30s or in adolescence the elevations of arterial pres *sure are transitory and subside promptly on* rest and minor reorientation of habit and attitude In its later stages the elevations of arterial pressure are more severe more last ing more resistant to minor modes of treat ment Finally the levels of pressure even at bed rest and under sedation tend to *stabilize at high levels* At any stage in the disease but as might be expected more commonly during the phases of per sistent and severe elevation of pressure there appear evidences of advancing arteri olar sclerosis which are reflected in dam age to the brain and in lesser degree *to the retina kidney* and other vascular beds With this go signs of damage to the function of the myocardium In a small per centage of patients essential hypertension is manifest as the syndrome of malignant *hypertension" in which the progress of* vascular damage is catastrophically acceler *ated with predominance of damage in the* renal vascular bed The same syndrome of accelerated arteriolar damage may be pre cipitated by other hypertensive disease states

The so called "secondary" hypertensions i e the hypertensive states of known or sus *pected origin can be classified according* to their causes as (1) neurogenic (2) endo crine (3) vascular and (4) renal As ex amples we note the hypertension in chronic porphyria as of presumptive neurogenic origin the hypertension and nephrosclerosis of Cushings syndrome, adrenal cortical

umor and adrenal medullary pheochromo ytoma as of endocrine origin the hyper ension of coarctation of the aorta as a type f cardiovascular hypertension and that of

ind diagnosis lies in the fact that for ex ample cases of pheochromocytoma and some with unilateral renal disease can be cured by surgical removal of the offending organ

The hypertension of aortic arteriosclerosis s of particular significance in considering he treatment in hypertensive vascular dis ase The increase in arterial pressure is largely if not entirely systolic It is due to a failure of the aorta which has become in elastic to expand and adapt its capacity to the blood ejected from the heart during its beat There is consequently an abrupt rise in systolic tension in the large arteries as this blood is forced into them on its way to the arterioles The extent to which systolic pressure rises depends on cardiac rate and cardiac output and in the last analysis most of all on stroke volume Consequently anything which tends to change stroke vol ume or cardiac output tends to have a paral lel effect on systolic tension Thus it is not paradoxical but entirelv logical that this form of hypertension in which the large arteries are least elastic is also the form in which the levels of systolic tension fluctuate most widely Cardiac output in intact human beings is predominantly under nervous con trol but varies also with metabolic rate tissue demands and other factors Therefore it is a common experience that mild meas ures such as rest reassurance and sedation and control of obesity which tend to de crease cardiac output often have dramatic results in decreasing arterial tension in el derly people It is this responsiveness of pressure levels in arteriosclerotic hyperten sion which has led so many unwary clinicians into unwarranted therapeutic claims Simi

the 50's transient increases of systolic ten sion occur which as time goes on become persistent at least during casual measure ments The diastolic pressure is little if at all increased The underlying disease is a generalized arteriosclerosis There are to be found therefore evidences of arteriosclerosis in the heart brain and kidneys But this disease has a slow rate of progress Conse quently although vascular accidents can occur without warning most of these people live to nearly a normal expectancy of life

The treatment of this condition is basically the treatment of old age and of vascular complications as they appear Many of the

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rtension

below

Essential Hypertension Just as the first step toward treatment in arterial hyperten

tension has been made its treatment again depends on further subclassification This subclassification is made from the state and kind of disease and its rate of progress

First of all there is the "prehypertensive" the youth with transitory elevation of arterial tension and usually other signs of vasomotor instability Essential hypertension has ap peared often among his ancestors In the present state of knowledge it seems likely that many of these will sooner or later de velop the disease in an established form The problem is to make its appearance come later rather than sooner Perhaps the best that can be done is to aid these people in orientation in life situations which will not place excessive demands on them and to counsel them toward the adoption of a serene and stable point of view

Next is the patient whose hypertension is persistent over long periods who shows minimal evidences of advancing vascular disease in the heart brain eyes or kidneys and who believes himself to be in good health Among these is a group whose pat tern is one of emotional instability of anxiety and of central nervous disequilib rium. This form of essential hypertension is called provisionally "neurogenic" One group of these patients constitutes the "hy pertensive diencephalic syndrome" de scribed by one of us This condition is

characterized by episodic discharges of emotional energy, evidenced by elevations of arterial pressure, weeping, blushing, of a macular spotty type, on the upper chest and neck, sweating, gastro intestinal activity, and other signs of autonomic release, including

tachycardia, "nervousness," sweating and frequently elevated basal metabolic rates (to levels of about + 20 to + 30) many of these patients are subjected to thyroidectomy, or receive antithyroid drugs, and, of course, without benefit A point in differential diagnosis is the level of the plasma cholesterol which, in these patients, is not decreased as it would be in hyperthyroidism Still another group of patients with early hypertension of seeming "neurogenic" origin are people who by racial and social constitution are emotionally labile and active, and whose resistance to pain or distress is low

The symptomatology of patients with hypertension of apparent neurogenic origin is varied and often dramatic Fortunately, the rate of progress of arteriolar and cardiac damage in patients of this sort is usually slow, possibly because the blood pressure is not persistently elevated These patients more than others tend to do well on general therapeutic measures, and many respond poorly to more drastic procedures, such as sympathectomy

Next there is the large group of patients whose disease is almost free of symptoms until perhaps some complication such as congestive cardiac failure or apoplexy or the onset of nocturia or hematuria draws them to the physician's office The problem of evaluating the nature and degree of vascular disability and the rate of its progress is especially urgent in these, since signs of progressive damage will tend to change the orientation of treatment This evaluation consists of a thorough examination which includes inspection of the retina and retinal vessels, measurement of heart size, an electrocardiogram, and measurement of maximal urinary concentrating power by the Addis test With these data to form the base line, the physician can estimate the rate of progress, or rejoice in the stabilization or recession of the disease at later examinations

Finally there are the patients noted above who show the syndrome of malignant hypertension, characterized by destructive arterial and arteriolar changes with retinal hemorrhages and papilledema, weight loss, hypertensive encephalopathy, cardiac failure, and progressive renal damage with hematuria and proteinuria In these, decision as to treatment must be made instantly and before vascular damage has become irreparable

General Measures Both patient and physician tend too much to neglect measures of treatment of hypertensive disease which are general and most of which fall under the definition of the basic hygiene of life The neglect is perhaps due to a wish that there would be some specific which will take care of everything which there is not Fortunately, however, general measures have great value in slowing the rate of progress of essential hypertension in all but its most severe form

A prime point is the decision of the patient to come to terms with his disability, so that he recognizes that, in order to prevent invalidism he must channel his activities with due regard to his condition This channeling is in the direction of moderation in work, and in play, and, if there is to be excess, let it be only in rest and recreation The basic aim is to secure a serenity and equanimity of mood, purpose, and action which will protect the patient from undue stress of mind or body

His work should be limited well within the borders of fatigue It should in most cases be noncompetitive It is a difficult decision for men and women who feel themselves in the best of health and productivity to lay aside some of their ambition for power and responsibility in order to protect themselves and their home, but it is often a necessary one We do not suggest that the patient should retire from his work and shut himself up making baskets—which would almost certainly make his condition much worse We mean simply that he should, as far as pos

technics and skills

Most patients will approach the problem of a rerouted existence in better spirit if they

can be brought to understand something of the nature of their disease There are vast stores of misinformation on the topic avail able from both quack and lay circles The physician who refuses counsel and inquiry exposes his patient to the menace of these, without any gain for himself It is usually much better to encourage the patient to ask questions and to answer them fairly and honestly. The physician may be aided in this educational program by prescribing for the patient a manual on hypertension intended for lay use Perhaps the only exception to the free and full provision of information is the answer to the question "And how is my pressure today?' This question is perhaps the best lead into a general discussion of the nature of the disease, of the variability of arterial pressure, and of the impossibility of measuring progress from single determinations And from such a discussion may come still more understanding and co operation

The specific problem of dietotherapy is dealt with below As far as diet enters into the general measures of control of hypertension, it is merely by the patient's extending to this aspect of life, as to every other, his general program of moderation He should eat less, especially when he is overweight He should perhaps be told that a 1 per cent

tea, tobacco, and alcohol, and of sexual inter course

The program of recreation is dependent on the individual's interest He should at least forego violent physical exertion and extremes of competition, seeking constructive and satisfying diversion without any particular achievement

Specific Measures POTASSIUM THIOCYANATE This salt has three actions that are use

able headache The latter is its most useful action The blood level should not be allowed to exceed 12 mg per cent and the usual therapeutic range averages 8 to 12 mg per cent Often as good results are achieved with somewhat lower levels The dose is that required to achieve this level Enteric coated pills should be avoided and the thiocyanate blood level should be determined in a competent laboratory rather than by short cut methods which often yield highly inaccurate results

If toxic manifestations occur, such as maculopapular rashes, confusional states, or goiter, the drug should be immediately dis continued

EXCESSIVELY LOW SODIUM DIETS The use of low sodium diets has recently been revived, but now the restriction is even more severe, not more than 200 mg of sodium be ing allowed daily This level is extremely difficult to attain in most patients and is al together impractical for some

The results in our patients have been only moderately encouraging At least 10 to 15 per cent show a significant fall in arterial pressure and some feel better Administration of salt to these patients is associated with a rise in blood pressure It appears that there is some direct association between the change in salt content of the diet and the height of the arterial pressure in these par ticular patients

Occasionally, circulatory collapse occurs from the severe salt deprivation, hence the treatment has potential dangers These can be exaggerated because most patients when not in the hospital under rigorous supervision do not keep their salt intake below 0 5 gm

Those of us who remember the era when low salt diets were being indiscriminately prescribed for hypertension recall that at times some lowering of pressure occurred ap parently as a consequence of the low salt in take But at that time, the intake almost never fell below 1 gm of sodium chloride It thus remains to be determined whether the drastic restriction now suggested is really *necessary At best relatively few* patients will be benefited from drastic salt restriction, but for these, it may well be worth the effort

The use of amberlite resins has been sug gested as a shortcut to a salt-poor diet It is much too early to recommend their general use Potentially, they may do serious damage by removing other important constituents from the gastro intestinal tract

RICE DIET The Kempner rice diet and

protein content, which in the Kempner regime is less than 20 gm and in the assumption that other foods contain unidentified toxic substances not present in rice, which embarrass the kidneys Two hundred and fifty to 350 gm of rice (dry weight) are taken daily All fruits are allowed except nuts, dates, avocados, dried or canned fruit, or fruit derivatives to which substances other than white sugar have been added Not more than one banana may be taken a day White sugar and dextrose are allowed ad libitum on the average, a patient takes about 100 gm daily, but if necessary, as much as 500 gm may be used Tomato and vegetable juices are not allowed Usually no water is given and the fluid intake is limited to 700 to 1000 cc of fruit juice per day Supplementary vitamins are added—vitamin A, 5000, D, 1000 units, thiamin chloride 5 mg, riboflavin 5 mg, niacinamide, 25 mg, calcium pantothenate, 2 mg Some form of iron is desirable Rest in bed is neither necessary nor desirable Weight may decrease markedly during the first 20 days

The diet should be continued without modification according to Kempner, until those conditions which were the indication for its use have disappeared Then small amounts of nonleguminous vegetables potatoes lean meat or fish (prepared without salt or fat) may be added

Nitrogen equilibrium is said by Kempner to be maintained in spite of the 20 gm protein content of the diet This has been denied by others (Schwartz and Merlis) Blood nonprotein nitrogen is lower than in normal or fasting human beings, i e, 27 as compared with 84 mg per 100 cc and urea nitrogen 14 1 mg before the diet and 7 8 mg after Hypercholesterolemia decreases markedly with the rice diet Two hundred of 284 patients with hypertensive vascular disease (70 per cent) had cholesterol concentrations of at least 220 mg per 100 cc, 132 exhibited a decrease to normal levels Free cholesterol and cholesterol esters decrease on the rice diet in about the same proportion There was a decrease of 99 per cent of the sodium in the urine, a 4 3 per cent decrease in serum sodium, and an insignificant increase in potassium concentration

The amount of protein given is less than the minimum for maintaining equilibrium estimated by several other investigators Indeed, actual measurement of nitrogen balance on the rice diet by Schwartz and Merlis showed it to be negative over several months But one of their subjects, whose hypertension seems to have been severe, was also much improved by it Still, there is no conclusive evidence that severe restriction of animal protein is of real value in hypertension except as it becomes necessary with the advent of renal failure

Kempner's indications for use of the rice diet consist of all serious instances of acute and chronic glomerulonephritis, heart failure which does not respond to the customary salt restriction and drugs, arteriosclerotic and hypertensive vascular disease with cardiac, cerebral, retinal, or renal involvement, uncomplicated hypertensive vascular disease when a more liberal regime, weight adjustment, restriction of activities, sedatives etc have failed It is suggested the diet be tried before sympathectomy is considered

Our own experience with the rice diet has been limited to some 50 patients Some of them would not stay on the diet because of its monotony Among those who did so after a prolonged control period, effects on the blood pressure have not been so impressive as when the diet was started shortly after coming under our care A fall in renal blood flow in some has occurred which so far has seemed reversible The eyegrounds of one patient may have cleared as the result of the diet, but this is uncertain for a variety of reasons Thus, it is our view that the rice diet deserves much more careful study

The divergent conclusions reached by different investigators lead only to the conclusions (1) that the problem is still in the investigational phase, and (2) that the investigations should be performed seriously and with every possible safeguard One of the essential safeguards least employed is an [illegible] the face

physician contact Casual blood pressure readings over even many years, however constant they may be, do not replace as controls frequent measurements before and during the periods of dietary control Another factor in prescribing the diet is the patient's en

thusiasm for it Often he can only be persuaded to it by promises of relief or threats of serious complications which few physicians can conscientiously subscribe to Still, some encouragement may be necessary, for it is only the rare patient who will take a detached and scientific view of a rigid dietary scheme

The effects of weight loss due to the diet have not been adequately evaluated European experience during the war, as well as common clinical observation, suggest that these play a much more important part in determining the decrease in arterial pressure than deprivation of animal protein and provision of protein of vegetable origin

Sympathectomy Three types of sympathectomy are now being practiced, the dorsolumbar operation of Smithwick, the *splanchnic nerve resection and* ganglionectomy of Peet, and the "total" sympathectomy of Grimson The Smithwick operation currently has the greatest popularity

While there has been much work on the nature of the changes produced by these operations, the problem has received no satisfactory solution As matters stand, it can only be said that in some patients the operations lower blood pressure along with both subjective and objective evidence of clinical improvement Unfortunately, it must be added that of the many tests proposed for patient selection, none have proved serviceable We are left then with no alternative but to make an arbitrary choice of candidates according to experience

Our selection is largely limited to two groups of patients those with rapidly advancing vascular disease, and those with early or even moderately advanced malignant hypertension We do not feel justified in operating on young people with essential hypertension in whom the rate of progress of the disease is not known Within this rather arbitrary framework we expect about 10 to 15 per cent among the essential hypertensives to show marked improvement, 30 per cent to show moderate improvement, 40 per cent to show subjective improvement, and the remainder to be without benefit Indeed, in a few patients almost complete remission has occurred, lasting for periods up to 3 years, seldom more

It should never be forgotten that there is some danger connected with the performance of the operation, and therefore it cannot be recommended lightly

The fact now seems to be established that when a marked fall in arterial pressure occurs as the result of operation, objective betterment in the electrocardiographic pattern, size of the heart, and appearance of the vessels in the eyegrounds usually follows There is no evidence that the denervation of the kidneys causes any direct increase in their excretory efficiency though with improvement in the general conditions of the blood vessels some increase in urinary output may be noted

Kidney Extracts The reasons for the search for substances in the kidneys which might lower blood pressure need not concern us here Extracts of kidneys have been *prepared which lower blood pressure and* cause improvement in the clinical condition of patients But the mechanism by which these extracts act is entirely unknown

Three possibilities currently present themselves (1) the pyrogenic and so called "nonspecific" effects associated with the injection of foreign proteins, (2) the presence of a substance inhibitory to the contraction of blood vessels, (3) the production of antirenin, (4) the presence of angiotonases

do not achieve the same result as the active renal extracts The presence of inhibitory substances is demonstrated by the inhibition of adrenalin and angiotonin when kidney extract is injected intravenously into anesthe-

renin, it is possible, though as yet undetermined, that this may be part of the action Although kidney extracts contain angiotonases, they are probably not concerned in their activity since we found 6 years ago that extracts rich in them were not active in patients

It is the belief of a few investigators that certain types of extracts of kidneys have these beneficial effects, but none to date has been able to prepare an altogether suitable extract Such a search is naturally a tedious and expensive job, since patients must be the

test objects and nothing is known of the chemical nature of the substance sought

There is some evidence which suggests but does not prove some degree of specificity Kidney extract will reverse the intrarenal hemodynamic change usual in many cases of hypertension to a more normal one Further, cardiac output will be elevated in hypertensive patients when the mean pressure falls

It is quite clear that work along this line

prematurely

VITAMIN A As the result of the clinical report of Villaverda and Pena, large amounts of vitamin A have been administered to hypertensives in this country But our results have shown clearly that vitamin A of itself, *even in great amounts does* not lower arterial pressure, although it sometimes improves renal function In hypertensive animals, some samples of fish body or liver oils seem to lower arterial pressure The investigation of this phase of the problem has not progressed sufficiently far to justify an opinion as to its value

RUTIN In 1860 rutin was isolated from buckwheat but it was not until recently that it has received clinical trial The latter was [illegible] to vitamin [illegible] some to be [illegible] d capillary [illegible] hemor

Reports on the value of rutin are highly contradictory In no small measure this is due to the wide variability of the results of the various tests of capillary fragility Indeed, at present it seems fair to indicate that none of the tests have been studied sufficiently carefully nor has the consistency of the results been demonstrated Little or nothing is known of the natural history of increased capillary fragility

Several authors have believed rutin prevents or cures the hemorrhages in diabetic retinitis, and if it had the desired effect on the capillaries and if hemorrhages result from increased fragility, this would appear to offer opportunity for successful treatment The more recent and careful articles find rutin of no value in the treatment of diabetic retinitis

Some time ago, rutin was suggested as a

treatment of a group of hypertensives in whom he believed he had demonstrated increased capillary fragility The fragility in many cases became normal It is not clear *what, if any, effect this had on the course of* the disease

Next, rutin was used in the hope that cerebral hemorrhage might be avoided on the theory that hemorrhage is due to capillary bleeding There seems to be no cogent evidence that this is so Since it is impossible with present methods to know when cerebral hemorrhage is going to occur, the problem *of studying the prevention becomes one of* the greatest difficulty At present there is no reason whatever for prescribing this drug for the prevention of cerebral hemorrhage despite drug house literature urging such indiscriminate use

The most significant evidence that rutin has some pharmacologic action comes from its use in experimental animals in preventing or reducing the hemorrhagic lesions induced in dogs by single large doses of roentgen rays It may also be of some value in purpura hemorrhagica Despite the claim that it conferred protection in anaphylactic and histamine shock, this has not been substantiated by *recent* work

Clearly the widespread sale of this material on the basis of published evidence was most unwise The drug houses have presented *only the side of the picture which makes the* drug saleable, rather than that showing it to be of only minor or of no value in treatment of hypertension Unless better evidence is forthcoming rutin has no place in the management of the hypertensive patient

BACTERIAL PYROGENS IN THE TREATMENT OF MALIGNANT HYPERTENSION Daily administration of concentrated bacterial pyrogens, especially those from *B prodigiosus,* over periods of weeks to months, often causes remarkable clearing of the pathologic changes in the eyegrounds of malignant hypertensives Thus in a series of patients studied by

Taylor, Corcoran, Fertig and Page,* average arterial pressure (systolic and diastolic) was reduced from a mean of 126 to 100 mm Hg Papilledema disappeared in all but 2 and fresh exudates disappeared Improvement was also noted in the electrocardiogram and the heart size diminished

Except for the persistent elevation of arterial pressure, remissions have lasted for an average of 2 years Of the remaining 19 patients, 11 responded more briefly, while 8 showed no change All but 2 of these are dead and these 2 are presently under treatment

The greatest drawback in the treatment is that tolerance to the pyrogen usually appears in from 5 to 19 weeks, after which arterial pressure usually rose to the control levels but without reappearance of the malignant syndrome

It has not been possible to select those patients who will respond to pyrogen therapy Six patients who were virtually blind and 4 who had congestive failure responded favorably In general it appears that if renal excretory function is reduced by 50 per cent or more the response will be poor, or at least no more than temporary

This treatment must be regarded as experimental until more experience has been gained In view of the gravity of the disease the results so far obtained justify its further use when the patient can be under the daily care of the physician

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A C CORCORAN

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* These authors have recently advocated the use of pyromen (Baxter Laboratories) when the pyrogen treatment is to be used This is given in a single intravenous injection the first dose being 0 5 cc ... to 6 months —*Editor*

DISSECTING ANEURYSM OF THE AORTA

Various statistical studies suggest that about 90 per cent of patients die in the initial attack, although with continued and careful study and earlier recognition of the syndrome this almost hopeless outlook has changed considerably and it is likely that about 20 per cent now survive Many patients have lived for long periods after rupture Pathologists are acquainted with patients who show the so called double aorta due to a previously ruptured dissecting aneurysm with complete endothelialization of the new channel and adequate function

The author is impressed with the similarity of the picture of acute dissection of the aorta with rupture to that of extensive myocardial infarction from thrombosis or from the less frequent and less accepted coronary spasm The former early hopelessness in the management of acute coronary thrombosis has given way to a high measure of promise in the efficacy of studied therapy The same effort should now be trained on the syndrome of ruptured aneurysm which is increasing in frequency with the known higher occurrence of hypertension A co-operative approach by internist roentgenologist, electrocardiologist and qualified vascular surgeon will bring about a more dependable

farction It has many or all of the features of complete or incomplete obstruction to the ingress of oxygenated blood to the heart, lung intercostal vessels, brain, abdominal viscera upper or lower limbs The first consideration is to relieve the agonizing pain and secure rest for the patient This may be accomplished by full doses of morphine or pantapon or similar preparations In patients known to be sensitive to morphine, pantapon

would seem preferable It may be necessary to give morphine in a dosage of ½ to 1 grain (30 to 60 mg) and pantapon in a dosage of ⅔ to 1 grain (40 to 60 mg), and such medication should be continued at regular intervals in an attempt to obtain complete physiologic rest Both may be combined with full dosage of atropine Vomiting calls for a substitution at once of narcotics known to be

ture is followed by a rather classical picture of acute aortic insufficiency with consequent final pulmonary engorgement and right heart dilatation Oxygen in full concentration is indicated This may best be accomplished by placing the patient in an oxygen tent although if, as is seen occasionally, the patient is distressed by the emotional tension of be

tial bed rest The patient should be protected by adequate and competent nursing so that all exertion is kept at a minimum Nursing care must extend around the clock if the patient is to receive the maximal protection from extension of the process The period of rest should be comparable to that advised in patients with severe myocardial infarction Absolute rest should continue for at least 6 to 8 weeks much restricted effort for another 6 to 8 weeks and gradual resumption of activity over another period of 6 to 8 months It is of course recognized that such limits are clearly arbitrary but not prohibitive if we are to increase the percentage of cured cases

Undoubtedly a high degree of angiospasm is present in the major vessel of the arterial tree when dissection is initiated The process is well understood in smaller vessels of the arterial tree and the same process must exist in this major vessel Angiospasm explains in part the tumultuous picture of early aortic tearing seen in the overwhelming pain suffocation and shock For this reason it is reasonable to suggest that adequate intravenous doses of papaverine be given slowly This medication can be given in the dosage of ½ to 1 grain (30 to 60 mg) repeated as indicated by the failure to relieve pain evidence of advancing ischemia and the persistence of sweating pallor, shock, and similar symptoms

The author can see no dependable reason for giving anticoagulants in this condition Our hope is to provoke thrombosis rather than increased fluidity, at least so far as the major vessel is concerned Whether vitamin K, vitamin C, or thromboplastic drugs can or will accomplish a measure of help is problematical

In a considerable number of patients, rup

cuff may be of service in supporting an otherwise acutely overdistended though insufficiently filled arterial system

In the presence of cardiac decompensation adequate doses of digitalis are indicated but we doubt the value of quinidine

For the first few days following rupture a liquid easily absorbed diet is necessary The introduction of large amounts of fluids into the vascular system is contraindicated A sensible balance between fluid intake by mouth and by the intravenous route is in order Plasma and blood transfusions have been suggested by many, but here again it is unlikely that either plasma or whole blood is the answer to the problem

Part of the difficulty incident to rupture of a dissecting aneurysm comes not from the dissection alone but from the compromise of the main aortic lumen by the pressure of a column of blood behind the intima not unlike the subintimal and medial hematomas described by Wartman in coronary thrombosis The relief of this blockade by the reestablishment of an ostium into the main channel is worthy of more than passing interest Congenital heart disease was long regarded as beyond surgical attack while today it is almost commonplace Since the introduction of antibiotics and the rapid advances in the technic of anesthesia, surgical attack on the heart and its blood vessels gives promise of an extension to this type of treatment for dissecting aneurysms Two complications of rupture of dissecting aneurysm merit surgical thought In various studies one third to one half of the cases had perforation into the pericardial sac with death due to hemopericardium, cardiac tamponade and acute compressive myocardial failure Early aspiration of the widening peri

cardial area with vigorous surgical attack may some day yield results of real value It is also known that in 20 to 30 per cent of these cases of rupture of a dissecting aneurysm perforation occurs into the pleural cavity with resultant rapidly increasing compression of the lung by hemothorax Here mere aspiration of fluid blood will accomplish nothing and more radical and dramatic effects might be produced by blockade of the bleeding area with coagulants It is certain that more vigorous surgical attack should be referred to the aneurysms which dissect into the abdominal vessels and occlude the vessels to the limbs and other structures since here undoubtedly part of the difficulty is again a mechanical blockade of the main lumen

Most of the recorded cases of ruptured dissecting aneurysm of the aorta occurred in patients who have had manifest hypertension Adequate treatment of the hypertension may prevent the development of a dissecting aneurysm and its subsequent rupture Certainly any patients with chronic hypertension marked sclerosis and widening of the arch of the aorta who have given any suggestion of dissecting aneurysm should be cautioned against overexertion both physical and emotional Bronchoscopy is clearly contraindicated in the presence of a suspected ruptured aneurysm

LeRoy H Sloan

ORTHOSTATIC (POSTURAL) HYPOTENSION

The typical syndrome of orthostatic hypotension is characterized by a marked fall of blood pressure and usually a relative bradycardia in the upright position impairment of sweating impotence and accentuation of symptoms in hot weather The condition is frequently associated with certain diseases of the central nervous system but may occur independently of any recognizable central nervous system disease In the latter or primary type of orthostatic hypotension the site of the primary defect is thought to be in the hypothalamus although this has not been definitely established

Although the pathogenesis of this syndrome is by no means entirely clear defects in the control of reflex sympathetic vasomotor function and cardiac rate in the upright position have been considered generally to be the most important factors Some observers feel that the fault lies in failure to maintain adequate venous return to the heart in the erect posture as the result of pooling of blood in the lower extremities (MacLean and Allen MacLean et al) Although this concept has not been generally accepted evidence would seem to indicate that such pooling of blood is a contributory factor in the symptom complex A decrease of blood volume and hemoconcentration has been demonstrated in the upright position and it has been suggested that abnormal filtration rates aggravate the circulatory disturbance (Hallock and Evans)

The treatment of orthostatic hypotension is not satisfactory and at best is only palliative When present any associated disease of the central nervous system should receive appropriate treatment These patients must keep their activities at a minimum during hot weather and avoid standing still for long periods

Various mechanical procedures such as the use of tight abdominal and leg binders sleeping in the "head up position and shifting the feet and shuffling movements while standing seem to lessen the tendency to decrease the blood pressure and may even suffice in an occasional case with mild symptoms Some patients object strenuously to the use of binders especially in warm weather

The use of the various vasoconstrictor drugs has been reported to be of benefit in some cases Ephedrine sulfate or neosynephrin hydrochloride may be administered several times daily in ⅓ grain (20 mg) dosage If amphetamine sulfate is used it is best to give ⅙ to ⅙ grain (5 to 10 mg) every 3 to 4 hours *Combinations of these* drugs may be used at the same time We have not been impressed with the value of these drugs in the treatment of orthostatic hypotension since their effects are transient at best and usually disappear over a period of time The same appears to be true of epinephrine hydrochloride either in aqueous or in oil solution

Brilliant results with the use of desoxycorticosterone acetate and sodium chloride have been reported If desoxycorticosterone acetate is used it should be administered

weight gain The administration of 2 to 5 gm of salt daily is usually adequate Although our experience with the use of desoxycorticosterone acetate in the treatment of orthostatic hypotension has been limited to a few cases, the results have been sufficiently encouraging to warrant further trial of this form of therapy However, the potential dangers are considerable, especially when the drug is employed in conjunction

from the administration of sodium chloride alone

There is no satisfactory specific remedy for the anhidrosis Pilocarpine will produce sweating in the anhidrotic regions but its use is not practical Improvement of the reaction of the blood pressure to standing may be accompanied by return of sweating and sexual activity

RICHARD M SHICK
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PERIARTERITIS NODOSA

(Polyarteritis Panarteritis Necrotizing Arteritis Kussmaul Maier Disease)

Periarteritis nodosa is an inflammatory disease of the arterial system which involves chiefly medium sized and small arteries and arterioles The terms "polyarteritis" and "panarteritis" are considered to be more descriptive of this rather uncommon condition, for actually the disease process involves all coats of the artery and nodular lesions may be entirely absent

Although periarteritis nodosa generally is considered a fatal disease, spontaneous remissions and apparent cures may occur The course may be acute, subacute, or chronic and it may last from a few days to several years It is important therefore to exercise due caution in evaluating the results of any *therapeutic measures in this condition*

Actually there is no known definitive *therapy which* either prevents, or affects the course of, the disease Symptomatic treatment is all that can be offered It generally consists of measures directed toward the organ or set of organs involved in the disease process This must of necessity be extremely varied and is usually unsatisfactory

It has been reported that derivatives of sulfanilamide have effected a cure in some cases but in our experience neither the sulfonamides nor penicillin has been of any apparent value We have had no experience with streptomycin or the newer antibiotics *aureomycin and chloromycetin*, in the treatment of this disease, but we have no reason to believe that they would be of value

The possibility that some cases of periarteritis nodosa may be due to hypersensitivity has suggested the use of the antihistaminic drugs Although our results with the use of these drugs in a small group of cases have not been impressive, we feel that this type of *treatment warrants further trial*

The recent reports of the effects of the adrenal cortical hormone, 17 hydroxy-11-dehydrocorticosterone (cortisone) and of pituitary adrenocorticotropic hormone (ACTH) on rheumatoid arthritis and acute rheumatic fever are encouraging (Hench et al) It has been suggested that these compounds may be useful in the treatment of other so-called *diffuse collagen diseases*, including periarteritis nodosa It is hoped that a more adequate supply of these preparations will be available for use in these conditions in the near future

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TEMPORAL ARTERITIS

(Cranial Arteritis)

Temporal arteritis is a self limited febrile disease of unknown etiology in which the temporal arteries and occasionally other arteries of the cranial system are the seat of a necrotizing panarteritis The active and symptomatic phase of the disease lasts from 2 to 6 months, after which recovery occurs although occlusion of the involved arteries usually persists Relapses may occur and if visual impairment develops it is usually permanent

Treatment of temporal arteritis has not been successful Treatment of the active phase is mainly symptomatic and consists of the usual measures to relieve pain Salicylates 15 grains (1 gm) three times daily and

that the patient remain in bed for a few days and soak the toe in warm water two or three times a day

Corns and calluses should not be cut Local applications for the removal of corns and proprietary corn and callus removers should never be used It is much more important to select properly fitted shoes to overcome these deformities and when they do occur to apply corn pads and bunion pads to prevent pressure or to soak the foot in warm water several times a day to soften up the lesion and then gently remove the thick cornified layer of skin

Chiropody may be necessary in some cases but it should be done only by a competent chiropodist who has knowledge of the problems associated with occlusive arterial diseases Injudicious surgical treatment of such lesions often leads to painful ulcers which are difficult to heal

Exposure to excessive cold and excessive heat should be avoided Ice should never be allowed to come in contact with an ischemic extremity Electric pads and hot water bottles should never be used no matter how cold the feet become Such applications frequently result in painful ulcers which may take months to heal or never heal

The patient should be cautioned against the hazards of trauma At times this may be unavoidable If trauma does occur and there is even the slightest break in the skin the patient should be cautioned against the use of a strong antiseptic such as tincture of iodine All ointments or solutions containing phenol should be avoided

Fungus Control Trichophytosis should be treated by only the blandest of remedies Irritating ointments and solutions should never be used Potassium permanganate in a 1 9000 solution used to soak the feet twice a day is a safe and effective remedy Keeping the feet dry by bland dusting powders is advisable

Control of Lipemia The control of lipemia in the presence of arteriosclerosis obliterans is not satisfactory at the present time The low fat, low cholesterol diet is of questionable value may not be effective and may be difficult to adhere to for long periods Thyroid in subtoxic doses may be effective and choline chloride has been found of value in some instances

Control of Diabetes The exact status of the diabetes should be determined and should be kept under rigid control Since tissues of diabetic patients are notoriously susceptible to infection and since infections in ischemic feet and legs may be disastrous the control of the diabetes is especially important particularly in those who have arteriosclerosis obliterans

Control of Polycythemia. Polycythemia vera frequently leads to increased thrombosis in both arteries and veins To arrest any progress of the underlying arterial disease it is evident that polycythemia if it exists should be treated and controlled

Anticoagulants Heparin and dicumarol are not of much practical value in the prevention of thrombosis in chronic occlusive arterial diseases because of the difficulty of safe administration over long periods and the uncertainty as to when the next episode of thrombosis may occur If the patient is confined to the hospital however their use may be justified as 10 per cent of all patients will at some time during the course of their disease suffer from an acute arterial occlusion (Allen Kvale and Allen)

Procedures Used for Vasodilatation

Warm Environmental Temperature. One of the best procedures for maintaining vasodilatation is to place the patient in an environmental temperature of 80 to 85° F The use of a heated box in which the patient s extremities are protected from the heating elements and in which the temperatures do not exceed 90° F is another aid in producing vasodilatation (Allen Barker and Hines)

TABLE III

Procedures Used for Vasodilatation

(1) Warm environmental temperature general and local
(2) Heat or diathermy to uninvolved parts of the body
(3) Intravenous administration of foreign protein (typhoid vaccine)
(4) Intravenous administration of hypertonic sodium chloride solution
(5) Ethyl alcohol by mouth
(6) Papaverine
(7) Anesthetization of sympathetic nerves or ganglia
(8) Tetra-ethyl ammonium chloride
(9) Regional sympathetic ganglionectomy

Heat or Diathermy to Uninvolved Parts of the Body Vasodilatation can be produced by short wave diathermy applied to the trunk but it does not persist after the treatment has been discontinued and the method is therefore of limited value (Bennett et al)

Intravenous Administration of Foreign Protein The injection of a foreign protein can be a valuable procedure for producing temporary vasodilatation and also for relieving pain, but it should be used only in thromboangiitis obliterans (Barker) We prefer typhoid vaccine because of its availability, relatively standard strength, and ease of administration Any stock typhoid vaccine may be used and is administered intravenously two or three times a week. The first dose is usually 0 1 cc of the vaccine and this dose should be increased 0 1 cc with each subsequent injection, depending on the severity of the reaction

Intravenous Administration of Hypertonic Sodium Chloride Solution This method of treatment is still being used in some eastern clinics, but our experiences with it have not been encouraging Two hundred and fifty to 300 cc of a 3 to 5 per cent solution may be administered two to three times a week

Ethyl Alcohol by Mouth. Alcohol by mouth will cause significant vasodilatation but its effect is somewhat transient We use it almost routinely on all patients who are confined to the hospital for relief of pain and for sedation as well as for vasodilatation However, care should be taken that its use does not become an abuse, 2 ounces of whiskey two or three times daily is usually adequate

Papaverine This drug is of little value when taken by mouth When used intravenously, 1½ grains (0 1 gm), is particularly helpful in releasing arterial spasm

Anesthetization of Sympathetic Nerves or Ganglia As an agent in the treatment of occlusive arterial diseases, anesthetization of sympathetic nerves or ganglia is of limited value because the effect is too transient It is, however, of value in testing for the degree of possible vasodilatation

Tetra-ethyl ammonium Chloride In our experience, this drug is of little value in treatment but again it may be of use in test-

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This operation is gaining in favor as treatment for arteriosclerosis obliterans as well as for thromboangiitis obliterans Reasons are that the vasodilatation produced is essentially permanent and improvements in surgical technic have significantly reduced the surgical mortality rate and even morbidity The operation abolishes not only vasoconstriction but also sweating of the extremity, thus preventing excessive cooling of the skin as the result of evaporation of sweat Sympathectomy does not open arteries already occluded by an organic process and does not prevent the development of new occlusive lesions in arteries or veins, but it does provide maximal arteriolar dilatation, prevents secondary arteriolar spasm, which may occur after an acute arterial occlusion, and prevents gangrene in many patients It is by no means, however, a certain guarantee against gangrene

Sympathectomy should not be done in all cases of chronic occlusive disease In mild cases in which sufficient collateral circulation has developed over a period of years, the operation may not be justified In the more severe cases in which there is extensive ulceration or gangrene of the digits or of the foot and severe arterial insufficiency is present sympathectomy will be of little or no benefit In arteriosclerosis obliterans, care must be exercised in selecting the treatment, since in many instances the surgical risk is increased because of vascular lesions elsewhere in the body, particularly in the coronary and cerebral arteries, and because arterial thrombosis in the extremities may occur during the immediate postoperative period

Mechanical Methods for Increasing Circulation The pavex alternating suction and pressure machine was in favor shortly after its introduction several years ago (Herrmann) but at present has been almost abandoned We have discarded its use altogether

The intermittent venous compression apparatus likewise held favor for several years, but it is of doubtful rationale and is being used less and less

The Sanders oscillating bed, which is merely a modification of the old postural

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TETRA ETHYL AMMONIUM CHLORIDE In our experience this drug is of little value in treatment but again it may be of use in testing for possible vasodilatation in a dose of 1 cc (1 0 gm) intravenously

REGIONAL SYMPATHETIC GANGLIONECTOMY This operation is gaining in favor as treatment for arteriosclerosis obliterans as well as for thromboangiitis obliterans Reasons are that the vasodilatation produced is essentially permanent and improvements in surgical technic have significantly reduced the surgical mortality rate and even morbidity The operation abolishes not only vasoconstriction but also sweating of the extremity thus preventing excessive cooling of the skin as the result of evaporation of sweat Sympathectomy does not open arteries already occluded by an organic process and does not prevent the development of new occlusive lesions in arteries or veins but it does provide maximal arteriolar dilatation prevents secondary arteriolar spasm which may occur after an acute arterial occlusion and prevents gangrene in many patients It is by no means however a certain guarantee against gangrene

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exercises carried out by the patient seems to be helpful in many cases and is still being used by us It can be used for several hours each day or continuously for days or weeks There is no evidence that it produces vaso dilatation but it seems to be helpful in some cases of severe ischemia In our experience patients have obtained more relief from pain from this apparatus than from any of the other mechanical methods Any of the three are at best only a supplement to other forms of treatment

TABLE IV

MECHANICAL METHODS FOR INCREASING CIRCULATION

(1) Intermittent suction and pressure
(2) Intermittent venous compression
(3) Oscillating bed

Control of Pain The pain of intermittent claudication may be relieved in about 50 per cent of patients by the intramuscular injection of tissue extracts Their use may not be justified however in all cases of occlusive arterial disease when the sole symptom may be intermittent claudication since the patient s occupation may not require excessive walking and the distance that he can walk may be sufficient so as not to interfere with his activities When relief from intermittent claudication is desired however intramuscular injections of tissue extract may be used and may be successful Of the tissue extracts we use pancreatic tissue extract A specific plan of treatment varies but it is usually our custom to give 5 cc of deproteinated pancreatic tissue extract intramuscularly daily for 2 or 3 weeks then three times a week for the next 3 weeks and twice a week for another 3 weeks After a rest period of 1 or 2 months such a course of treatment can be repeated if it is considered necessary The use of tissue extracts alone in the treatment of pain of ischemic neuritis is ordinarily unsuccessful but it is generally used for this pain in conjunction with other forms of treatment

Many drugs have been used for relief of the various types of rest pain whether associated with ulcerative or gangrenous lesions or with the excruciating pain of ischemic neuritis These drugs are listed in Table V Aspirin 10 grains (0 6 gm.) together with whisky may frequently afford as much relief from pain as any of the other drugs If
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nay
to
opiates is not common but the possibility must be kept in mind always and the use of opiates must be kept at a minimum Barbiturates such as 0 1 gm of seconal may be used as necessary for the induction of sleep but it may be ineffective if pain is severe Generally the best plan is to get along as well as possible with as small amounts of the drug as possible and to discontinue its use when feasible

TABLE V

CONTROL OF PAIN

(1) Tissue extracts
(2) Barbiturates
(3) Salicylates
(4) Opiates
(5) Demerol hydrochloride
(6) Ethyl alcohol by mouth
(7) Anesthetization of peripheral nerves or nerve roots with alcohol or dolamine
(8) Surgical section or crushing of peripheral nerves

In some cases of ischemic neuritis benefit has been obtained by the injection of dolamine into peripheral nerves or sensory nerve roots although experience is insufficient for adequate evaluation of this procedure to date Injection of alcohol into nerve roots or peripheral nerves is not advisable though it has been advocated by Smithwick and White and by Scott and Morton Surgical section or crushing of peripheral nerves in the lower third of the leg (Laskey and Silbert) would seem to be a rational procedure for the relief of intractable pain in the foot or toes but results generally have been rather disappointing There is always the risk of nonhealing of the surgical incisions and if the pain is the result of ischemic neuritis section of the nerves in the region of the ankle will not relieve pain resulting from degeneration and fibrosis of nerves proximal to this point Our experience with these methods of treatment has generally been unsuccessful and it has usually been necessary to amputate the leg in the cases in which they have been used particularly when

ceration or gangrene of one or more of the toes, or the foot, has been present

Treatment of Ulceration and Gangrene The best treatment for ulceration and gangrene, as has already been mentioned, is, of course prevention This cannot be overemphasized It is still rather discouraging to realize that 50 per cent of all types of ulcerations and gangrene seen in arteriosclerosis obliterans and thromboangiitis obliterans might have been prevented by avoidance of mechanical chemical, and thermal trauma Minor avoidable injury, hot water bottles or heating pads ice packs, strong antiseptics corn cures, keratolytic agents, and irritating ointments or solutions are strongly contraindicated for ischemic tissues

TABLE VI

TREATMENT OF ULCERATION AND GANGRENE

(1) Prophylaxis avoidance of mechanical, thermal and chemical trauma
(2) Fungus control
(3) Warm soaks bland solutions
(4) Wet dressings bland solutions
(5) Ointments
(6) Tyrothricin locally
(7) Sulfonamides orally
(8) Parenteral penicillin
(9) Powdered erythrocytes
(10) Debridement of gangrenous tissue
(11) Amputation of digits
(12) Amputation of limb

The patient with gangrene or ulceration should usually be treated in the hospital One of the most important rules in the treatment of these lesions is to do as little as possible and to avoid any procedure which may have even the slightest possibility of producing more injury to tissue It is best to keep the patient constantly in bed with the leg in a horizontal position as much as possible Prolonged dependency of the leg may lead to edema and increased difficulty in healing Many patients with constant pain tend to keep the affected leg hanging over the edge of the bed since this seems to afford them some relief from pain This must be avoided or attempts at healing of the lesion will be unsuccessful

Warm (100 to 105° F) soaks in boric acid solution or weak (1 9000) solution of potassium permanganate for 10 or 15 minutes two or three times a day are probably about as efficacious in combating the infection usually associated with ulceration or gangrene as any other remedy The use of warm, but never hot, wet dressings may further facilitate drainage and hasten the loosening of sloughs When wet dressings are used, it is well to allow the ulcer or area of gangrene to be exposed to the air for an hour or so every 3 or 4 hours to avoid the maceration of tissue

Ointments are usually of little value There are few external applications which are bactericidal or bacteriostatic and still are not irritating to ischemic tissues An ointment containing 5 per cent sulfathiazole is not irritating and may be of some help in loosening an area of localized gangrenous or necrotic tissue

Weak solutions of tyrothricin (0 05 per cent solution) are bactericidal for some organisms and have a tendency to stimulate the growth of granulation tissue and epithelium This form of treatment may be alternated with other methods mentioned previously

The oral administration of sulfonamides and parenteral administration of penicillin alternately or in combination have been used to treat and inhibit the infection in ulcerative and gangrenous wounds The results of treatment with these drugs have been uncertain, but it seems to be the consensus that healing occurs more readily than before the use of antibiotics

When the ulcers have become clean powdered erythrocytes can be applied They have been effective in promoting healing in some cases It is well to alternate the use of powdered erythrocytes with either warm boric acid soaks or boric acid packs Encrustations may ensue after prolonged use of powdered erythrocytes, pocketing regions of pus which cannot drain until soaks or packs are used

Occasionally, gentle débridement of a gangrenous toe or portion of a toe, once it has loosened, will expedite healing This should be done only, however, after the gangrenous region has become well demarcated and has begun to separate spontaneously

Amputation of a toe may be undertaken if the gangrene is limited to the toe, if the collateral circulation appears adequate, and if

there is no infection in the base of the toe However, there is always the possibility that healing will not occur, that an ulcer will

necessary As a rule, amputations of the three middle toes are more likely to be followed by healing than are amputations of the first and fifth toes Amputations of toes are generally more successful in thromboangiitis obliterans than in arteriosclerosis obliterans Amputation of any finger in thromboangiitis obliterans has always been successful Parenteral antibiotic therapy before and after amputation has been of considerable help

and amputation of the leg will be necessary Transmetatarsal amputations are rarely successful If healing does occur, the remaining portion of the foot is rarely useful The best sites for amputation are through the midcalf region and through the middle third of the thigh The best test is for the surgeon to make his incision in the midcalf without a tourniquet If adequate bleeding occurs and the muscles appear to be reasonably healthy, then amputation can be completed at that site However, if little bleeding occurs and

putations

Newer Drug Therapy of Questionable or Temporary Value In the last few years several new methods of medical treatment have been advocated enthusiastically for chronic occlusive arterial diseases The results described by the proponents of these

TABLE VII

NEWER DRUG THERAPY OF QUESTIONABLE OR TEMPORARY VALUE

(1) Intravenous ether
(2) Histidine and vitamin C
(3) Priscol
(4) Vitamin E
(5) Intra arterial histamine

methods have not been uniformly confirmed Intravenous ether (Katz), histidine and vitamin C (Wirtschafter and Widmann), and intra arterial histamine (Mufson), have been reported as improving the circulation Weisman and Allen have been unable to show that either intravenous ether or histidine and vitamin C had any beneficial effect on the circulation We have had limited experience with intra arterial histamine, but our results to date have been disappointing Priscol or priscoline, 50 mg three times daily, has been shown to be a vasodilating drug (Grimson et al), but in our experience it has been rather ineffective in the treatment of occlusive arterial diseases The good results reported from treatment of occlusive arterial disease with vitamin E have not, to our knowledge, been confirmed

Summary The general principles to be used in treating occlusive arterial diseases have been grouped under the headings of (1) procedures used to arrest the progress of the disease (2) procedures used for vasodilatation, (3) mechanical methods for increasing circulation (4) efforts to control pain, and (5) treatment of ulceration and gangrene

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SUDDEN ARTERIAL OCCLUSION

(Arterial Embolism and Acute Arterial Thrombosis)

Sudden arterial occlusion is one of the most catastrophic complications of cardiovascular disease Its occurrence is always associated with the possible loss of the involved extremity and of the patient's life as well for amputation necessitated by severely *ischemic tissue* and gangrene is not without risk

Arterial embolism ordinarily produces profound effects on the arterial circulation (McKechnie and Allen) Such effects appear less striking in acute arterial thrombosis but are nonetheless important The resulting *ischemia is due in large part to spasm of the* collateral arteries induced by the presence of the embolus or thrombus If such ischemia persists for more than a few hours the intima of blood vessels beyond the site of occlusion is injured to such a degree that thrombosis occurs upon release of the arterial spasm Thus if *treatment is delayed* or inadequate the ischemia which originally was caused by mechanical obstruction of an artery by an embolus or thrombus and by arterial spasm eventually is the result of more diffuse intravascular thrombosis

In some instances the cause of the sudden arterial occlusion is not clinically apparent even after all available information has been considered Fortunately rational treatment of the arterial insufficiency resulting from occlusion ordinarily is not *dependent on* an exact determination of the cause except when embolectomy may be indicated

There are three important "don'ts" in the treatment of sudden occlusion of the arteries of the extremities namely (1) don't delay active treatment (2) don't elevate the involved *extremity* and (3) don't subject it to heat which exceeds 90° F (35° C) (Allen) To delay treatment means a poor prospect of recovery in those instances in which recovery will not occur *spontaneously* Elevation of an extremity after sudden arterial occlusion and the local application of heat are ill advised procedures The former augments the ischemia by further diminishing the flow of blood to the extremity while the latter may cause burns which may contribute *importantly* to eventual loss of the extremity

It has been estimated that in approximately 50 per cent of cases of sudden arterial occlusion of the extremities *gangrene* will develop if nothing but the simplest conservative treatment is carried out Better under

standing of the abnormal physiologic processes involved and the use of methods to correct them have yielded far better results than were obtained a few years ago when treatment was directed mainly to the local problem However it is difficult to evaluate *critically the efficacy of individual agents* because of the almost universal tendency to employ numerous measures in a justifiable endeavor to save the extremity

The relief of pain and of arterial spasm and the reduction of the coagulability of the blood are important considerations in the active treatment of sudden arterial occlusion *Morphine sulfate ¼ grain (15 mg)* should be given immediately to control pain The involved extremity should be placed in a dependent position When a leg is involved the head of the bed should be elevated when an arm is involved the patient should be placed in the semi Fowler position The

and a cradle with the temperature not to exceed 90° F open at one end may be placed over it

Because only part of the impairment of the arterial circulation is due to the primary occlusive process in the artery relief of the associated arterial spasm which may further compromise the circulation is of paramount importance One of the best ways of accomplishing this is to increase the environmental temperature The patient should therefore be placed in a room the temperature of which is approximately 90° F (32.2° C) Alcohol which is both an antispasmodic and an anodyne should be given as whiskey in amounts of 2 fluid ounces (about 60 cc) every 2 to 4 hours depending on the tolerance of the patient Papaverine hydrochloride may be given intravenously or injected directly into the artery proximal to the site of occlusion The usual dose of

Additional measures for inducing peripheral vasodilatation may be employed The Sanders oscillating bed may be helpful and should be used if available The use of reflex heat by means of a baker over the trunk or diathermy with the pads applied to the lower part of the abdomen and the lumbosacral region has some value Heat should never be applied directly to the involved extremity and except for preamputation anesthesia the use of refrigeration should be condemned for many limbs have been *lost by the injudicious use of such procedures* Spinal anesthesia or paravertebral anesthetization of appropriate sympathetic ganglia with novocain hydrochloride may be effective It may be necessary to repeat these procedures several times within 2 or 3 days if any response is to be maintained General sympathetic block with tetra ethyl *ammonium chloride and allied substances has* been advocated (Acheson and Moe) but we have not been impressed with the value of these drugs in the treatment of sudden arterial occlusion Since they may induce profound hypotension their use in such cases would not seem to be without hazard In our experience a warm room the injection *of papaverine* the use of whisky and the Sanders bed have been almost uniformly adequate

The use of anticoagulants has constituted one of the greatest advances in the treatment of thrombo embolic diseases in recent years They are needed in instances of sudden occlusion of arteries of the extremities to prevent propagation of the occluding thrombus or embolus to prevent extensive thrombosis of the collateral arteries and veins which may follow the release of the secondary vascular spasm and to prevent further thrombo embolism during periods when such complications may be imminent We use the two anticoagulants heparin and dicumarol The former produces its effect on the blood promptly while the latter does not produce an effect on the blood for from 24 to 48 hours We have used heparin both by continuous intravenous infusion and by intermittent intravenous injection The latter method has impressed us as being much simpler and just as effective as continuous intravenous infusion The use of depot heparin would be helpful but to date the

the side effects notably pain at the site of injection have precluded their use in many instances

We inject 50 mg of an undiluted solution of heparin intravenously every 4 hours until the dicumarol has become effective If the use of dicumarol is contraindicated the injections of heparin should be continued for several days

An initial dose of 300 mg of dicumarol is given orally about the same time as the first injection of heparin This is followed by 200 mg on the second day of treatment The subsequent dosage of dicumarol is determined by the level of prothrombin in the blood We attempt to maintain the prothrombin at about 20 per cent of normal If it is more than 20 per cent 48 hours after the initial dose 100 or 200 mg of dicumarol are given and the same dose is repeated each 24 hours when the level of prothrombin is more than 20 per cent Inasmuch as the administration of heparin may influence the prothrombin time the blood for this determination should be withdrawn not earlier than 3 hours after the last injection of heparin

If the prothrombin in the blood decreases to less than 10 per cent of normal or if there is evidence of bleeding as a result of prothrombin deficiency vitamin K should be administered intravenously in doses of 36 or 72 mg depending on the apparent urgency of the situation When bleeding occurs as the result of heparinization the intravenous injection of 50 mg of protamine may be indicated and in the event serious hemorrhage occurs during treatment with either heparin or dicumarol intravenous infusions of fresh whole blood should be given

The medical treatment of sudden arterial occlusion may be summarized as follows *(1) give an opiate to relieve pain* (2) induce arterial relaxation by the use of whisky by mouth an increased environmental temperature the oscillating bed if available and the intravenous or intra arterial injection of papaverine hydrochloride (3) diminish coagulability of the blood by the use of heparin and dicumarol The constant attention of a physician is required until the situation is relieved or the unfortunate outcome is established

If the afore mentioned procedures fail to produce significant improvement in the circulation within 8 or 10 hours surgical removal of the clot should be considered When embolectomy or thrombectomy is contemplated the use of dicumarol should be discontinued However we favor the continued use of heparin in such cases and if the surgeon wishes he may inject heparin directly into the artery proximal to the site of arteriotomy as soon as the incision has been closed

Ordinarily treatment with anticoagulants can be discontinued after 7 to 10 days However in certain instances of recurrent embolic arterial occlusions associated with chronic auricular fibrillation it may be advisable to continue the use of dicumarol indefinitely if attempts to restore and maintain sinus rhythm with quinidine have been unsuccessful

The subsequent treatment of an extremity rendered permanently ischemic as the result of a sudden arterial occlusion is the same as that of chronic occlusive arterial disease

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RAYNAUD S DISEASE

The patient should be reassured regarding the absence of serious organic disease of the blood vessels as well as the loss of extremities which should never occur in Raynaud s disease Adequate protection is of paramount importance This includes the use of warm clothing especially fur lined mittens and in some instances ear muffs and lined galoshes Moving to a warmer climate may be advisable in some cases Anemia if present should be corrected as well as any other conditions which are debilitating to the patient

Inasmuch as it is well known that nicotine produces vasoconstriction the use of tobacco may be expected to aggravate Raynaud s phenomenon and hence its use should be discouraged in patients with Raynaud s disease

A variety of drugs has been advocated for use in Raynaud s disease The mere enumeration of these would indicate of itself that *there is no medical treatment* of specific or even of great value The judicious use of mild sedatives during periods of increased nervous and emotional stress may be of some benefit Mild Raynaud s disease associated with the menopausal syndrome may

be benefited by the use of estrogenic substances and in occasional instances in which Raynaud s phenomenon is greatly aggravated during the menstrual period moderate relief of symptoms may follow the administration of these drugs The use of thyroid in instances of hypometabolism may be advisable although the effects of this treatment on the vasospastic disturbance have not been impressive

The use of nitrites papaverine and similar vasodilating drugs seems to have little if any effect on the course of Raynaud s disease The action of these drugs is transient and their effect is less impressive than that induced by the ingestion of alcohol However the use of alcohol in this d sease has its obvious limitations The use of some of the newer adrenolytic sympathicolytic and [illegible] little or no practical value in the treatment of Raynaud s disease We have had no experience with the use of the hydrogenated derivatives of ergot (Bluntschli and Goetz) but we doubt that these drugs will prove to be of much benefit in this condition The application of nitroglycerine ointment to the fingers of patients with Raynaud s disease may be of benefit in some instances but the effects of this treatment are variable and unpredictable and its use is purely palliative Acetyl beta methylcholine (mecholyl) chloride iontophoresis has been of little or no benefit in our hands

It is apparent from the foregoing discussion that medical treatment of Raynaud s disease is not satisfactory About all that can be said in summary is that reassurance of the patient is important so that an anxiety state will not develop that protection from the cold in every way possible is advisable and that estrogenic therapy in the female may be tried when seemingly indicated

Sympathectomy still remains the most satisfactory method of treatment in Raynaud s disease However the amount of disability resulting from the angiospastic disturbance should be considered carefully in the selection of patients for this procedure Sympathectomy would be ill advised in the mild and nonprogressive type of the disease In the moderately advanced stage of the disease it is advisable for the patient to try a season or two in a warm climate if possible before undergoing sympathectomy inasmuch as some of these patients may live fairly comfortably for years in a mild climate In the advanced stages of the disease in which painful superficial ulcers have developed on the tips of the fingers sympathectomy is justifiable and may be expected to result usually in the healing of the lesions and relief of pain This procedure however may not prevent the subsequent recurrence of trophic lesions or development of scleroderma

Sympathetic ganglionectomy with trunk resection is the operation usually performed at the Mayo Clinic (Allen Barker and Hines) The reason why lumbar sympathectomy generally produces more satisfactory results than cervicothoracic sympathectomy for Raynaud s disease is not clearly understood It may be because Raynaud s phenomenon and trophic changes are not as severe in the feet as in the hands or because of inherent difference in the reaction of the blood vessels or the vasomotor nerves in the lower and upper extremities There is evidence which suggests that preganglionic resections are more satisfactory than postganglionic resections although this point is still debatable Sympathectomy may be of temporary benefit in scleroderma with associated Raynaud s phenomenon However in our experience this procedure generally does not alter the course of the primary disease and is recommended only in cases in which the vasospastic disturbance is severe and incapacitating

The painful ulcers which develop on the tips of the fingers of some patients with advanced Raynaud s disease are treated in much the same manner as the ischemic ulcers associated with thromboangiitis obliterans

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LIVEDO RETICULARIS AND ACROCYANOSIS

Livedo reticularis is a vasospastic disorder characterized by a persistent bluish to bluish red mottling of the skin of both legs and feet which is more prominent on ex

posure to decreased environmental temperature The mottling involves the hands and arms to a less degree and may extend to the thighs and even the lower part of the trunk Ordinarily the condition is asymptomatic although some patients complain of coldness numbness paresthesias and dull aching of the feet and legs In severe cases ulcers may develop on the skin of the legs and in rare instances gangrene of the toes as the result of occlusion of the digital arteries has been observed

Although in most of the cases of livedo reticularis no treatment other than reassurance is required the avoidance of exposure to cold so far as possible and abstinence from the use of tobacco may be indicated in some instances A period of rest in bed together with medical and physical vasodilating procedures is advisable when ulceration or gangrene is present Sympathectomy has been employed with some success in a few cases

Acrocyanosis is a vasospastic condition characterized by painless and persistent coldness and cyanosis of the distal parts of the extremities and is closely allied to livedo reticularis The mechanism producing the vascular changes in these two conditions is not clearly understood but is generally considered to be that of arteriolar constriction with associated dilatation of the capillaries and venules Whether these phenomena are due to some local fault in the smaller blood vessels or are the result of a hyperreactive sympathetic nervous system is still a debatable question

The treatment of acrocyanosis has not been satisfactory However the condition is usually so innocuous that protection from cold is the only treatment necessary The use of acetyl beta methylcholine (mecholyl) chloride by iontophoresis has been advocated but in the majority of cases this is not necessary In the rare severe cases sympathetic ganglionectomy may be considered

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ERYTHROMELALGIA

(Erythermalgia)

Erythromelalgia is an uncommon vascular disorder characterized by intermittent burning pain associated with redness and increased warmth of the skin of the extremities The feet are usually involved and the symptoms are induced by exposure to increased environmental temperature are intensified by prolonged dependency and are relieved by cooling the affected parts

Erythromelalgia may occur primarily as in the idiopathic type or it can occur secondarily in association with a number of conditions and diseases notably polycythemia vera and hypertension It has also been observed in cases of gout organic neurologic disease and poisoning from thallium mercury or arsenic

The treatment of erythromelalgia is not uniformly successful When the syndrome is secondary to some other condition the treatment is that of the condition which produces it Of course the importance of avoiding anything that produces vasodilatation in the extremities should be emphasized Light weight shoes and socks or stockings should be worn and exposure to warm environmental temperature should be minimized Change of residence to a moderate climate may be advisable

Desensitization of the skin to warmth has not proved to be of much help in our experience However this method of treatment seems rational and probably warrants further trial Desensitization is begun by immersing the involved extremities in water at 30° C for 15 minutes twice daily for 2 or 3 days The temperature of the water is then increased 1 or 2° for another period of 2 or 3 days and this program is continued If symptoms occur when the temperature of the water is that which ordinarily provokes distress the course of desensitization is repeated

For reasons not clearly understood as little as 10 grains (about 0 65 gm) of acetyl salicylic acid may produce marked relief which may persist for as long as several days Relief has been noted following the injection or inhalation of solutions of epinephrine hydrochloride (Mufson) but we have not had much experience with this form of treat [illegible] ed to the

[illegible] ay be necessary to anesthetize the skin of the feet by section or crushing of the appropriate

peripheral nerves or by the injection of alcohol into them Sympathectomy also may be considered if relief of the distress is obtained by anesthetization of appropriate sympathetic nerves

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SCLERODERMA

(Acroscleroderma Acrosclerosis Diffuse Scleroderma)

Scleroderma is characterized by induration of the skin frequently associated with atrophy and pigmentation vasomotor disturbances and at times myosclerosis and calcinosis Three distinct types occur diffuse scleroderma acroscleroderma with Raynaud s phenomenon (acrosclerosis), and circumscribed scleroderma (morphea) Sclerodactylia which may develop in association with advanced Raynaud s disease of long standing is considered by some observers to be secondary to the circulatory disturbance and by others to be part of the syndrome of acrosclerosis

Scleroderma may involve any area of the surface of the body and also various visceral organs notably the esophagus and lungs However our remarks will be confined chiefly to acrosclerosis which is a syndrome characterized by scleroderma of the extremities face and thorax associated with Raynaud s phenomenon in the extremities and includes instances of primary sclerodactylia

In the treatment of scleroderma palliative measures may be of considerable value These measures are essentially the same as those employed in cases of Raynaud s disease without scleroderma and include (1) protection of the diseased portions against trauma and extreme environmental temperatures and (2) increase of peripheral circulation It is also important to increase the suppleness of the involved parts in order to delay hardening and contracture of the skin and subcutaneous tissues This is accomplished mainly by the use of physical therapy including heat and massage and the judicious use of contrast baths Emotional and psychic stresses should be avoided and the use of tobacco should be discouraged

The use of thyroid, pancreatic preparations and injections of posterior pituitary extract has been advocated (Oliver and Lerman) Our experiences with the use of these preparations as well as mecholyl

chloride by iontophoresis have been uniformly discouraging (Duryee and Wright) Prostigmine (neostigmine) may be of some benefit in increasing strength and a sense of well being and in mobilizing the stiffened muscles and joints in patients with mild or moderately advanced acrosclerosis The use of this drug both intramuscularly, 0 5 mg three to four times daily, and orally, 15 mg four times daily, in conjunction with papaverine, 0 1 gm, seems to be of value in some cases (O Leary)

The administration of the antihistaminic drugs in increasing doses to the limit of tolerance may be of some value in the early and edematous phases of the disease, and results with the use of androgens in a small group of cases have been somewhat encouraging to date Other methods of treatment of no or questionable value include the use of gold or bismuth, alpha tocopherol (vitamin E), dihydrotachysterol (A T 10), and the local application of various agents, including nitroglycerin ointment (Kierland)

Sympathectomy has been of limited benefit in the treatment of scleroderma The following situations may be considered indications for this procedure (1) minimal and slowly progressive acroscleroderma with associated Raynaud's phenomenon of moderate degree (2) moderate acroscleroderma with severe spasmodic pain in the fingers as the result of frequent and severe attacks of vasospasm (Raynaud's phenomenon), and (3) slight or moderately severe sclerodactylia with recurring painful fissures and ulcerations that have not responded to more conservative methods of vasodilatation Parathyroidectomy has been recommended on the ground that some disturbance of calcium metabolism may play a part in the pathogenesis of this disease This operation has largely been abandoned as useless in scleroderma

There is some reason to believe that the adrenal cortical hormone, 17-hydroxy 11 dehydrocorticosterone (compound E), and pituitary adrenocorticotrophic hormone (ACTH) may prove to be of value in the treatment of scleroderma and allied conditions (Hench et al)

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PHLEBOTHROMBOSIS AND THROMBOPHLEBITIS

The therapy of peripheral venous thrombosis has undergone many fundamental alterations during the past decade The role of secondary vasospasm in the causation of the symptoms and the complications of peripheral venous thrombosis was first recognized by Albert and Leriche The prevention of the formation of intravascular blood clots by the use of natural and synthetic anticoagulants was shown to be practical by Jorpes Murray, and Link, while the localization of blood clots to an extremity by the ligation of large veins was first practiced by Homans and by Arthur Allen These diverse methods of treatment have made available valuable data on which we have based our practical measures for the management of patients with peripheral venous thrombosis

This discussion would be incomplete without a short summary of those important clinical aspects of the problem which must be kept in mind if the process of venous thrombosis and its complications are to be treated successfully

General Considerations Massive pulmonary embolism which is the dreaded sequel of peripheral venous thrombosis, is a threat to the patient's life following any major surgical operation, any trauma to the extremities, any protracted serious illness, or at the termination of pregnancy The physicochemical alterations in the blood which initiate such venous thromboses do not differ greatly from those incidental to the normal process of coagulation except that, under ordinary conditions blood does not clot within the normal blood vessels during life

Many terms have been used to describe the various phases of venous thrombosis The most commonly used terms are thrombophlebitis, phlebothrombosis, bland or silent venous thrombosis and just plain venous thrombosis From the pathologic standpoint it is logical to assume that the simplest variety of venous thrombosis should be unassociated with inflammation, consequently the clot will be loosely attached to the wall of the vein Such a condition has been called *phlebothrombosis* (Ochsner and DeBakey) On the other hand, the intravascular clotting of blood associated with and dependent on inflammatory changes in the wall of the vein, with the clot usually firmly attached, has been called *thrombophlebitis* There are numerous phases to the reaction in the wall of the vein after intravascular clotting of blood takes place Bland intravascular clots may extend from the deep veins of the leg into the iliofemoral segments where perivenous reaction to the clot may

the development of a bland, nonadherent thrombus extending proximally from such an area of thrombophlebitis The differentiation, therefore, of thrombophlebitis from phlebothrombosis is largely of academic interest, for in clinical practice these two phases of venous thrombosis are frequently seen in the same patient at the same time

Much has been written recently about the importance of the veins of the calf muscles as the main source of pulmonary emboli, yet clinical experience has indicated that other sources, especially the veins of the pelvis and abdomen, and particularly the chambers of the right side of the heart, should not be overlooked as silent but important sources of blood clots which may be carried to the lungs and lodged as emboli Massive pulmonary emboli often have their origin from such sites of thrombosis The incidence of small latent blood clots in the pelvic veins, periprostatic, and perivesical plexuses is high and we believe such clots frequently initiate ascending venous thrombosis after slight trauma or after some physicochemical changes cause a sudden rise in the coagulability of the blood

Pulmonary embolism has been considered by some clinicians as a catastrophe which makes its appearance without special warning in an otherwise healthy patient who has almost recovered from some surgical operation Such a concept of pulmonary embolism is archaic, for it is well established that this complication of venous thrombosis is even more frequent in patients who have been confined to bed for some reason other than a surgical operation This is particularly true of patients over 40 years of age who have been confined to bed because of chronic heart disease or fracture of some long bone of the body

The important considerations for the clinician however, center around the prevention of the formation of blood clots within peripheral veins or, if they have already formed how they may be prevented from being extended or transported to vital parts of the body The early recognition of peripheral venous thrombosis is therefore essential to effective therapy

Prevention of Venous Thrombosis Prolonged stagnation of blood in the various venous plexuses of the body favors the formation of intravascular thrombosis Many factors influence the return of blood from the peripheral veins The maintenance of normal negative pressure within the abdomen and thorax with the elimination of all forms of mechanical obstruction to the return flow of blood must not be minimized The muscles of the calf region are pressed against the mattress when patients lie in bed and there is abnormal pressure over the adductor regions in fat individuals whose thighs press together while lying in bed It would be poor clinical judgment to give active treatment for a weak heart muscle and

limiting the extension of venous thrombosis in the extremities

Antidotes for Heparin and Dicumarol If an emergency operation is necessary while the clotting time is prolonged by the administration of heparin, the effect of the heparin can be neutralized immediately by the intravenous administration of protamine sulfate One cubic centimeter of 1 per cent protamine sulfate solution will neutralize at least 15 mg of crystalline heparin

If the prothrombin concentration is decreased by the administration of dicumarol, the effect of this drug can be abolished by the transfusion of freshly drawn citrated whole blood or by the intravenous administration of 40 to 60 mg of menadione bisulfite, or by the injection of Vitamin K_1 oxide

Contraindications to Use of Anticoagulants The presence of any blood dyscrasia which produces a hemorrhagic tendency or any form of purpura is considered a contraindication to the use of either heparin or dicumarol Patients with definite hepatic insufficiency or hepatogenous jaundice, especially if associated with prothrombin deficiency, should never be given dicumarol Patients with renal insufficiency, active tuberculosis, open wounds, or potential bleeding surfaces should be given heparin or dicumarol with great caution Dietary or nutritional deficiency should preclude the use of either heparin or dicumarol

LOCAL DERANGEMENTS OF THE CIRCULATION Elevation of the extremity is the most effective means of reducing the edema of the tissues in patients with venous thrombosis The high protein content of the lymphatic fluid from the nodular thrombophlebitic extremity makes it essential to keep the swelling at a minimal level lest the fluid clot and the resulting cellular reaction produce irreparable changes in the tissues

Roentgen Therapy The pain of subacute and chronic phlebitis can be lessened and the edema reduced by small doses of roentgen irradiation Doses of 200 r may give a serious general reaction in patients with acute phlebitis Between 30 and 40 per cent of an erythema dose (125 to 135 r) with heavy infiltration may even cause some rise in temperature over the veins For the most beneficial results in mild forms of thrombophlebitis, we recommend not more than 80 r through filters of 2 mm of aluminum and 0 25 mm of copper, to be given at one week intervals

Anesthetization of Regional Sympathetic Ganglia This procedure is commonly referred to as a "paravertebral block" and has been widely used to give relief of swelling and pain in the acute phases of thrombophlebitis On the basis of experimental observations, Albert suggested the procedure to Leriche for clinical application In 1934 Leriche and Kunlin described the method of blocking the regional sympathetic ganglia (LI, LII, LIII) with 10 to 15 cc of 2 per cent solution of procaine hydrochloride at each level, to overcome the secondary vasospasm associated with acute postoperative thrombophlebitis Their reports indicate that most of their patients were relieved of their symptoms by this paralysis of the vasomotor nerves to the affected extremity In 1939 Ochsner and DeBakey confirmed these results and suggested that the method of treatment be applied more widely

Proper anesthetization of these ganglia will usually relieve pain reduce the edema of the part, and restore the arterial pulsations to a normal level The beneficial effects of this simple therapeutic procedure in the chronic phase of iliofemoral thrombophlebitis which has caused considerable chronic [illegible] have been [illegible] iod of dis [illegible] *thrombo*-phlebitis can usually be shortened by repeated anesthetization of the regional sympathetic ganglia

PREVENTION OF TRANSPORTATION OF FRAGMENTS OF CLOT The interruption of the deep veins of an extremity to prevent transportation of fragments of a blood clot to the lungs is still not widely accepted

In all cases of acute ascending venous thrombosis in the great saphenous vein of the thigh, the saphenous vein should be ligated and divided at its junction with the femoral vein before the process of thrombosis ascends to that level Such superficial venous thrombosis usually ascends progressively and may enter the common femoral vein and produce signs of deep venous thrombosis In the chronic forms of thrombophlebitis where the common femoral vein had previously been occluded, the added danger from ascending

thrombosis in the great saphenous vein is then slight.

In patients with *acute venous thrombosis* which involves the deep veins of the calf of the leg or a popliteal vein in which there is no evidence of periphlebitis or reflex vaso motor phenomenon indicating involvement of the iliofemoral segment the ligation and division of the superficial femoral vein are occasionally indicated We prefer anticoagu lants alone but if the venous thrombosis is ascending the combination of ligation of the superficial femoral vein and the use of anti

after operation

Ligation of the inferior vena cava should be reserved for patients with suppurative thrombophlebitis or pylephlebitis arising from disease in the pelvis

The common femoral veins the external iliac veins or the common iliac veins should not be ligated because the collateral venous circulation is so poor after the occlusion of these veins that chronic edema of the ex tremity usually results

Prevention of Recurrent Attacks Car diac function must be kept efficient and all factors which produce stasis of blood in peripheral veins must be eliminated Varicose veins should be removed by surgical opera tion and not obliterated by sclerosing so lutions Edema of the extremities must be controlled by properly fitted elastic stockings

We have found that the use of small doses of dicumarol (25 to 75 mg) daily for many months has been indicated in some patients with recurrent attacks of venous thrombosis Prothrombin time determinations are made at frequent intervals until the value becomes stabilized at about 50 per cent of normal

We have not observed serious bleeding or

of peripheral venous thrombosis are most disabling and may be prevented by pro longed use of dicumarol

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daily. Use of injectable liver extracts containing added pteroylglutamic acid is not recommended because of the small amount of pteroylglutamic acid given the patient, particularly in maintenance therapy when a single injection is administered only once a month.

It is probable that within a short time, vitamin B_{12} (possibly synthetic) or a microbially produced substance, probably identical with vitamin B_{12} (Stokstad et al.) will supplant liver extract in the treatment of pernicious anemia. Early reports indicate that these substances are fully effective in inducing and maintaining hematologic remission and in controlling the neurologic disorder. Vitamin B_{12} in intramuscular doses of less than 0.005 mg. daily or in single doses of as little as 0.003 mg. have induced hematologic remission. Further study is necessary to establish proper dosage finally.

Although patients with pernicious anemia invariably have achlorhydria, the administration of hydrochloric acid to all patients is not required, and does not contribute to recovery from the anemia. However, any patient with achlorhydria may have digestive disorders which can be helped by the administration of acid. Thus, hydrochloric acid is indicated in patients with pernicious anemia only if symptoms of digestive disorder are present. Among these are either diarrhea or constipation, "gas in the stomach," belching, and sense of fullness after eating.

If it is used, hydrochloric acid should be given as the dilute U.S.P. preparation in doses of 2 to 5 ml. well diluted in 150 to 200 ml. of water, either 15 minutes before eating or taken with the meal. The acid causes some corrosion of teeth, both natural and artificial, so it should be ingested through a glass tube or straw and the mouth should be rinsed with water afterward.

Hydrochloric acid is available in tablet form as glutamic acid hydrochloride, each tablet being equivalent to 0.67 ml. on being dissolved in the stomach. These tablets are less irritating to some patients than the solution of hydrochloric acid and are especially convenient when the patient is eating away from home. They are considerably more expensive than an equivalent amount of dilute hydrochloric acid.

Iron is of no value in the treatment of pernicious anemia, but it is not uncommon for patients with pernicious anemia to have iron deficiency in addition. This becomes manifest after the initial response with liver extract has been obtained. It is then observed that the hemoglobin increases more slowly than the erythrocyte count and determination of the indices shows values below normal for the mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

In this event iron therapy should be administered as described below. It should be borne in mind that the iron is being given to treat an iron deficiency anemia associated in this instance, with pernicious anemia. Iron is of no value in treating pernicious anemia itself.

In the presence of infection, such as cystitis or pyelitis, for example, the response to treatment is less rapid and less complete than in uncomplicated cases. The infection should be treated by the appropriate method and liver extract should be administered at more frequent intervals using the erythrocyte and hemoglobin levels as guides.

Macrocytic Anemia of Pregnancy. Pregnant women may develop a macrocytic anemia with megaloblastic hyperplasia of the marrow. These cases are uncommon in the author's experience. They respond well to therapy with either liver extract or pteroylglutamic acid (Moore et al.). Since the latter is fully effective when given orally, it is probably the treatment of choice. It should be given in doses of 20 mg. daily. Therapy can be discontinued when the pregnancy has terminated.

Much more common in pregnancy is a mild or moderate anemia, slightly macrocytic (mean corpuscular volume 100 to 105 cu. microns), not associated with megaloblastic hyperplasia of the marrow. These patients will not respond to liver extract, pteroylglutamic acid, or other forms of therapy. The anemia is not severe enough to be serious and usually corrects itself within several weeks after termination of the pregnancy.

A bone marrow examination is essential, [illegible] osis of true [illegible] associated [illegible] of the marrow.

Macrocytic Anemia of Nutritional Deficiency Individuals eating inadequate diets presumably deficient in vitamin B_2 may develop macrocytic anemia associated with megaloblastic hyperplasia of the marrow Such cases have been described by Spies in the mountain country of southern United States and sporadic cases associated with alcoholism morphine addiction or other conditions limiting dietary intake are seen occasionally Administration of an adequate diet will eventually produce recovery from the anemia Administration of either liver extract or pteroylglutamic acid as in pernicious anemia permits of more rapid recovery however When the anemia has been corrected and the patient is eating an adequate diet continued treatment is unnecessary

Macrocytic Anemia of Infancy Macrocytic anemia with megaloblastic hyperplasia [illegible]

infants fed solely or chiefly on certain proprietary milk substitutes which are presumably deficient in some hematopoietic substance These infants also frequently show other evidence of malnutrition and often have mild infections which in themselves are not serious The anemia responds well to pteroylglutamic acid (Zuelzer) while purified liver extracts and vitamin B_2 have been ineffective in at least some of the cases Five to 20 mg daily cause rapid remissions to occur Again unlike pernicious anemia continued treatment is unnecessary once the anemia has been corrected and a proper dietary regimen has been established This includes the addition of supplemental foods to the diet in addition to diluted cow s milk or proprietary milk substitute

Myxedema Hypothyroidism is commonly associated with anemia which is usually macrocytic but in which there is little varia [illegible]

administration of thyroid substance is followed by a slow improvement in the blood although complete restoration to normal may not occur for 3 to 9 months

The simultaneous occurrence of pernicious anemia and myxedema has been observed (Wilkinson) In such cases neither liver extracts nor thyroid are effective when given alone but a good response is obtained when the two are given together

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APLASTIC AND PRIMARY REFRACTORY ANEMIA

Hypoplastic Anemia Hypoplastic (or aplastic) anemia may result from exposure to toxic agents or may occur without recognizable cause

Hypoplastic anemia is especially apt to develop after exposure to benzene or compounds containing the benzene ring, certain of the heavy metals and certain drugs These anemias are apt to be sudden in onset and rapidly progressive with marked thrombocytopenia and leukopenia in addition to the anemia

There is no specific effective therapy The offending agent should be removed Liver extract folic acid iron or other such therapy has no beneficial effect The patient should receive repeated transfusions with 500 ml of compatible blood given at intervals sufficiently close to maintain the erythrocyte count at around 3 000 000 per cubic millimeter

Death in these patients is generally the result of hemorrhage associated with the thrombocytopenia The [illegible]

count with multiple transfusions minute hemorrhages into vital organs still cause death There is no completely satisfactory manner to combat the bleeding tendency Blood transfusions help to control it but the effect is not complete and is transient Recently protamine and toluidine blue (Allen and Jacobsen) given intravenously have been claimed to have some effect. They can be given in doses of 2 to 3 5 mg per kilogram of body weight diluted in 500 ml of normal saline While these compounds are efficient neutralizers of heparin their effect in severe thrombocytopenias is doubtful and variable since hyperheparinemia probably is not a component of the bleeding tendency in these circumstances

The leukopenia predisposes to infections

which can usually be combated successfully with penicillin or the sulfonamides It is de sirable to administer penicillin prophylacti cally whether obvious infection is present or not Intramuscular doses of 20 000 units of penicillin in aqueous solution at intervals of 3 hours or single doses of 300 000 units of one of the long acting preparations at in tervals of 24 hours is recommended Oral preparations given at intervals of 3 hours are satisfactory if the dose used is two to five times that of the intramuscular route

While the great majority of these patients die within a short time blood transfusions should be administered steadily as long as life lasts since a small percentage finally makes a complete recovery

Hypoplastic anemia also occurs without discernible cause This is seen usually in older people (50 years of age and older) Its onset is slower and often the thrombo cytopenia and leukopenia are not as marked Again bleeding is the controlling factor and if this is absent as is not infrequently the case such patients can be kept alive for many years with repeated transfusions It is desirable if feasible to administer single blood transfusions of 500 ml at weekly in tervals after the patient has received enough blood to raise the erythrocyte level suffi ciently to alleviate symptoms of anemia (be tween 3 000 000 and 4 000 000 per cubic millimeter) The regular transfusions of blood at short intervals maintain the blood at a fairly constant level and prevent the severe anemia which develops if several transfu sions are given on consecutive days with long intervals between courses of transfu sions

Although such treatment may prolong life from a few months to several years throm bocytopenia ultimately develops and death occurs in spite of transfusions

Achrestic Anemia Another refractory anemia described mainly in the British liter ature is the so called achrestic anemia The incidence of this type of anemia in the United States is apparently low While the blood and bone marrow findings resemble those seen in pernicious anemia there is no re sponse to liver extracts A questionable re sponse has been observed after treatment with folic acid (Wilkinson) Blood transfu sions should be given as indicated by the degree of the anemia

Myelophthisic Anemia This term is ap plied to the anemias associated with diseases involving the bone marrow such as leukemia lymphosarcoma Hodgkin s disease and plasma cell (multiple) myeloma In some of these the bone marrow is more than nor mally cellular owing to the presence of ab normal numbers of the pathologic cell In other cases such as plasma cell myeloma the cellularity of the marrow is greatly de creased In any event the resulting anemia is of the hypoplastic type and will not re spond to therapy with liver folic acid iron or vitamins

The primary disease should be treated as far as possible and in the chronic leukemias radiation therapy is followed by marked im provement in the anemia Other than this blood transfusion is the only treatment As in true hypoplastic anemia thrombocyto penia with the attendant hemorrhage is often an outstanding feature and may be fatal

It should be emphasized that liver ex tracts pteroylglutamic acid iron vitamins and all other known medications are with out benefit in any of the hypoplastic anemias discussed in this section and there is no rationale for their use

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HYPOCHROMIC ANEMIA

Iron Deficiency Anemia The great ma jority of hypochromic anemias are the result of insufficient iron stores This occurs in in fancy because of iron deficiency in the mother during pregnancy Growth increases demand for iron so that anemia may develop in adolescence It occurs in adult women as the result of excessive menstrual flow or in creased demands for iron during pregnancy It occurs in either sex at any age as the result of chronic blood loss It should be emphasized that apart from pregnancy hypochromic anemia in the adult almost in variably represents blood loss It is not al ways possible to demonstrate the site of bleeding at the time the patient presents him self since the bleeding may have stopped Thorough search of the patient for possible

causes of hemorrhage especially cancer should be made This includes roentgen studies of the lungs and gastro intestinal and urinary tracts if other methods of investigation fail to reveal a potential source of bleeding

In treatment the bleeding should be eliminated by suitable procedures Other than this treatment consists of the administration of inorganic ferrous salts by mouth Practically any iron compound will be utilized in hemoglobin production if given in sufficient amount Ferrous sulfate is probably the most popular preparation used although ferrous gluconate is gaining in popularity Both have the advantages of being readily absorbed less irritating to the gastric mucosa than many other iron salts and are inexpensive

Either one should be used in doses of

ately after meals to obviate or decrease gastric irritation In the case of ferrous sulfate enteric coated tablets are available and desirable

There is considerable difference of opinion as to the necessity of hydrochloric acid for the absorption of iron It is probable that iron is more readily absorbed in the presence of hydrochloric acid but good results are obtained in most patients with achlorhydria without the administration of acid

The parenteral administration of iron is seldom if ever indicated and is undesirable because of the frequent occurrence of toxic reactions In the event that orally administered iron cannot be tolerated or cannot be absorbed because of diarrhea as occurs in certain cases of ulcerative colitis for example blood transfusions are preferable to parenterally administered iron salts In the event that intramuscular administration of iron is considered desirable iron and ammonium citrate is probably as safe and as effective a preparation as any It should be started in small doses for example 10 mg the first dose 25 mg 2 days later 50 mg in another 2 days and then if no undesirable reactions result 100 mg given at intervals of 2 or 3 days Any single dose should not exceed 100 mg

Infection Chronic infectious diseases are associated with hypochromic anemia but will respond little or not at all to administration of iron salts Treatment of the infection and administration of blood transfusions as indicated represent the only effective therapy

Cancer Cancer likewise is often associated with hypochromic anemia If blood loss has occurred from the site of the cancer administration of iron salts will cause some rise in the hemoglobin although it is frequently impossible to restore it to normal More often the hemoglobin levels off at 9 5 to 10 gm per 100 ml and will not respond to further iron therapy If it is desired to raise the hemoglobin level further blood transfusions must be used

Miscellaneous Other hypochromic anemias usually the result of congenital or inherited defects also occur and are important

these anemias are often accompanied by splenomegaly removal of the spleen does not have a beneficial effect on the anemia The only indication for splenectomy is discomfort caused by the enlarged organ

Substances Other than Iron in Treatment In general it should be emphasized that liver or liver extracts have no beneficial effect on iron deficiency anemias Preparations containing mixtures of liver iron and sometimes vitamins are widely advertised They are much more costly than simple iron salts and add nothing to the effect of the iron Their use can only be considered as ill advised "shot gun therapy

While copper is undoubtedly necessary for the formation of hemoglobin it is probable contrary to certain published claims (Fowler and Barer) that copper deficiency does not exist in adults True copper deficiency has been recognized rarely in children There is no indication for the administration of copper to adults Furthermore unlike iron salts which are not toxic in thera

including molybdenum has been advocated (Neary) In the writers opinion convincing

evidence that this augments the effectiveness of iron has not been presented

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HEMOLYTIC ANEMIA

Congenital Hemolytic Anemia Congenital hemolytic anemia (also called congenital or familial hemolytic icterus) is a well defined syndrome associated with spherocytosis of the erythrocytes, splenomegaly, and bouts of jaundice and fever Since it is congenital it is often recognized in infants and children Milder cases may escape detection until adult life, however, sometimes being diagnosed during a pregnancy when the obstetrician seeks an explanation for the presence of anemia

Splenectomy is curative in these patients so far as the symptoms are concerned While the congenital defect spherocytosis, is not significantly altered after splenectomy, the abnormally shaped erythrocytes are no longer destroyed more rapidly than normally, so that excessive hemolysis stops and the blood values return to and remain permanently at normal levels

Acute Hemolytic Anemia An acute hemolytic anemia, often called *Lederer's anemia*, most often occurs in infants or young children, although it has been observed in adults As seen in children, it most commonly appears 1 to 2 weeks after a mild illness frequently an upper respiratory infection The onset of the anemia is sudden and there may be a rapid drop in the erythrocyte count to low levels in a day or *two*

Blood transfusions, are usually followed by rapid cessation of the hemolytic process In many cases, a single blood transfusion is effective in causing improvement More commonly three to six transfusions given at daily intervals or as frequently as necessary as judged by the degree of anemia, are required Recovery is complete and relapses seldom occur If the patient is a child, any single blood transfusion should consist of about 20 ml per kilogram of body weight

Some cases have been observed to become chronic Splenectomy has been said to have been of value in these patients, as in the occasional patient with the acute process who does not respond to blood transfusions There is some dispute about this, but since there is no treatment other than blood transfusions, splenectomy should certainly be offered to those patients who fail to respond after transfusions The subject has been thoroughly reviewed by Damashek

Hemolytic Anemia with Serum Agglutinins Other types of hemolytic anemia associated with spherocytosis of the erythrocytes are occasionally encountered It has been claimed that abnormal serum agglutinins can be demonstrated in certain of these cases (Loutit and Morrison) The pathologic mechanism of the disorder is not understood and splenectomy is not of value Supportive treatment with blood transfusions represents the only available therapy

Sickle Cell Anemia (Thalassemia) Sickle cell anemia and Cooley's anemia (thalassemia, erythroblastic anemia) both involve excessive hemolysis of erythrocytes In both diseases the erythrocytes are characteristically flatter than normal and contain small

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should be given as required by the degree of anemia present In both diseases the spleen may become so large that splenectomy is justified in order to relieve symptoms produced by the size of the organ

In sickle cell anemia anoxemia should be avoided since this increases the tendency for sickling of the erythrocytes and accelerates the rate of hemolysis These individuals almost invariably develop hemolytic crises following inhalation anesthesia even though *precautions to avoid anoxemia* are taken The crises so induced can usually be combated successfully by multiple blood transfusions since only the cells of the patient are hemolyzed, the transfused cells surviving in the recipient s blood a normal period of time

Reactions to Transfusion with Incompatible Blood There are various types of secondary hemolytic anemias One type results from the administration of incompatible blood, either on the basis of the A and B agglutinogens or because of the administration of Rh positive blood to Rh negative individuals who have been sensitized to the Rh factor with resultant production of anti

bodies In either case the diagnosis should be made quickly As soon as any combination of symptoms including chill fever pain in the lower back or a sense of oppression in the chest is manifest the transfusion should be stopped immediately

It has been customary to institute alkali therapy as promptly as possible The free *hemoglobin present in the blood precipitates* as casts in the kidney tubules and it is well known that hemoglobin is more soluble in alkaline solutions than in acid However whether alkalinization of the urine actually prevents formation of hemoglobin casts in the kidney tubules and if it does whether the more important kidney insufficiency which results from lower nephron nephrosis is altered in any way is doubtful (Lucke) The clinical impression persists however that some benefit may be expected from alkalinization A suitable plan includes the intravenous administration of 250 ml of M/6 sodium lactate with initial oral administration of 15 gm of sodium bicarbonate During the next 24 hours oral doses of 5 gm of sodium bicarbonate should be given at intervals of 3 or 4 hours and the intravenous administration of sodium lactate can be repeated The urine should be maintained at an alkaline pH of 7 0 or greater until the benzidine test for hemoglobin becomes negative usually 24 hours or less unless the nephrotic syndrome develops In this event oliguria occurs with urine of low specific

greater than the urinary output If parenteral fluids are used excessive amounts of sodium chloride solutions must be avoided since sodium retention promotes edema A solution of 5 per cent glucose is satisfactory

Hemolytic Anemia Associated with Cold Agglutinins Recently hemolytic anemia resulting from the presence of abnormal cold agglutinins in the serum has been described (Finland et al) The cold agglutinins so called because they can be demonstrated only at temperatures lower than that of the body are especially apt to be found in the serum of patients with atypical nonbacterial ("virus") pneumonia although they are found occasionally in other patients Although the spleen is usually palpably enlarged splenectomy is of no value in altering the course of the anemia Blood transfusion is hazardous since the transfused erythrocytes are also destroyed by the patient s serum Most patients eventually recover although deaths have been reported If the anemia becomes so severe that blood transfusions are considered imperative every ef*fort must be made to keep the blood at* body temperature (98 6° F 37° C) during transfusion This may be accomplished by placing hot water bottles around the con

the blood is given must also be kept warm since the superficial surface veins used in transfusion have a temperature lower than 98 6 ° F (37 ° C) Even with these precautions transfusion is often followed by a severe hemolytic episode so that the erythrocyte and hemoglobin levels may be lower following transfusion than before

The patient should be protected against chilling even after recovery Chilling even by immersing the hands or arms in cold water can precipitate hemolytic crises

Hemolytic Anemias Due to Drugs or Toxins Certain drugs or toxins may be responsible for hemolytic reactions These include the sulfonamides certain coal tar derivatives and lead compounds. Phenyl hydrazine and its derivatives cause hemolysis In Italy the raw fava bean or its blossom may produce a severe hemolytic anemia in sensitized individuals Infections with hemolytic streptococcus and staphylococcus and with malaria may be associated with hemolytic anemia Withdrawal of the drugs or removal of other causes and administration of blood transfusions as dictated by the degree of anemia result in disappearance of the hemolytic process and recovery of the patient

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ERYTHROBLASTOSIS FETALIS

(Hemolytic Disease of the Newborn)

The term erythroblastosis fetalis is used to identify an acute hemolytic disease of the newborn which may assume varying clinical forms fetal hydrops *icterus neonatorum*

and congenital anemia of the newborn This disease begins in utero, often resulting in stillbirths but may not be evident until after the first few days of the infant's life Briefly stated, the sequence of events in the pathogenesis of erythroblastosis is as follows the mother is Rh negative, her erythrocytes being devoid of the Rh factor of Landsteiner and Weiner, the father is Rh positive, and the fetus is Rh positive, having inherited the factor from the father Fetal erythrocytes enter the maternal circulation by some mechanism as yet not clearly defined This stimulates the production of anti Rh iso antibodies in the mother which diffuse into the fetal circulation via the permeable placenta and produce within the fetus an antigen antibody reaction, with hemolysis of erythrocytes, and other manifestations of the disease

The physician is often required to discuss with his patient whether pregnancy is contraindicated by Rh factor incompatibility, or, if it has already occurred, whether it should be terminated It is well known that an affected baby is not produced in all such cases It is extremely rare for the first pregnancy to produce an erythroblastotic baby, and in many instances this does not occur even after multiple pregnancies This is explained by several factors (1) Not all Rh negative *women respond to the Rh antigen with anti*body production (2) it is thought that the normal placental barrier in most women cannot be penetrated by Rh factor bearing erythrocytes (3) 57 per cent of Rh positive men are heterozygous, which means that such individuals upon mating with an Rh negative female will have offspring half of whom are Rh negative and only half Rh positive

To summarize this particular problem it has been calculated that 12 per cent of all marriages represent Rh incompatability, but only one of 15 such marriages results in erythroblastotic infants

An important consideration in the prophylaxis of erythroblastosis is the determination of the Rh status of all women in the adolescent or childbearing age group, prior to any blood transfusion By giving an Rh negative female Rh positive blood, sensitization is achieved, which increases the hazard of producing offspring with erythroblastosis fetalis When a woman has been previously sensitized by transfusion or intramuscular injection of blood, the disease is more apt to

positive fetus

Once an erythroblastotic infant is born however, treatment should be directed toward maintaining the hemoglobin at a satisfactory functional level until the hemolytic process subsides This requires the use of blood transfusions Current opinion is that group compatible, Rh negative blood should be used Rh positive blood (especially the father's blood) is unsatisfactory because anti-Rh agglutinins from the mother which have not combined with its own erythrocytes are still circulating in the infant's blood stream, or are present in the infant's tissues As a result additional blood destruction may take place, tissue reactions may occur and an increase in the severity of the disease results

If group specific Rh negative blood is not available there are several alternatives Group O, Rh negative blood with low titer of anti a and b iso-agglutinin may be used with safety The use of the anti a and anti b Witebsky substance assures neutralization of the agglutinins in the serum of group O *blood*

The use of maternal erythrocytes has been advocated for transfusion of the infant the maternal serum being discarded because of the presence of Rh antibody It was recommended that the cells be washed several times in sterile isotonic saline solution, then resuspended either in sterile isotonic saline or plasma from an individual of the same blood group as the mother Study of the preservation of red cells has indicated however, that such manipulation, particularly resuspension in saline, greatly attenuates the red cells so that their life span in the recipient is short Furthermore even five washings of the maternal erythrocytes fail to remove all of the Rh antibody and an appreciable amount is given to the recipient with the cells

In addition, erythroblastotic infants often have low serum proteins so that the administration of serum, in addition to cells is highly desirable

In any event, it has become apparent that

as soon as a diagnosis of erythroblastosis has been made, blood transfusions should be given immediately The illness may be considered to be a medical emergency, and the sooner therapy is instituted the better are the results The blood must be given intravenously, not intramuscularly If the mother gives a history of having had previous ery throblastotic babies, the disease may be anticipated even before the child is born, and under such circumstances a prophylactic transfusion can be given into the umbilical vein before the cord is cut and tied

The recommended quantity of blood to be transfused is 10 cc per pound of body weight (Wiener and Wexler) Thus, the av erage erythroblastotic infant will receive 75 cc of the proper blood intravenously as soon as possible after the diagnosis is made It has been recommended that this be repeated the following day In the average case, this [illegible]

destroyed This is sufficient to carry the in fant over the period during which the Rh antibodies are being eliminated, and often for as long as a month the donor's erythro cytes are the only ones the infant possesses as shown by differential blood grouping tests

Another, and probably better method of treatment has been described more recently (Wiener et al , Wallerstein, Diamond) Nu merous names have been applied to this pro cedure, including exchange transfusion, re placement transfusion and exsanguination transfusion Briefly stated, the procedure consists of bleeding and transfusing the in fant simultaneously, or alternately bleeding and transfusing small amounts of the prop- [illegible]

transfusion method the mortality rate remained relatively high In addition, trans fusions do not remove the agents responsible for the hemolysis in the infant but only supply the infant with functional erythrocytes to tide it over the period of severe anemia resulting from the hemolysis of its own cells Further, the toxic products of hemolysis, either stromal or chemical, may be lethal to infants exhibiting only mild anemia Death of the baby may result from a hemorrhagic diathesis which does not seem to be influenced by repeated blood transfu sions It has been postulated that adult blood might increase the danger of hemoly sis in erythroblastic babies by activating an otherwise inactive Rh antibody The more recent studies of the role of the liver and certain other tissues in the pathogenesis of erythroblastosis show that hemolysis should, if possible, be prevented The replacement transfusion is designed to do this

Replacement transfusion, if it is to be at all successful, must be carried out within 24 hours of the infant's birth Ideally, an erythroblastotic baby should be anticipated, and the treatment performed immediately after birth The treatment should take no longer than 60 to 90 minutes during which time, in the average sized infant, one blood volume or 250 cc of blood are removed, and 300 to 350 cc administered With this procedure, only 25 per cent of the original Rh positive erythrocytes remain in the infant s circulation If 400 cc of blood are removed, and 450 to 500 cc administered, 87 per cent of the infant s blood volume is replaced If 900 cc of blood are removed and 1000 cc administered a replacement of about 98 per cent occurs During the procedure two to four doses of 0 2 ml (2 mg) of heparin should be administered, the last dose midway through the transfusion so that little anticoagulant effect remains at its termination The blood vessels most frequently used in carrying out the replacement are the radial artery or sagittal sinus for bleeding and saphenous vein for infusion, or the umbilical vein for either or both

It must be borne in mind however, that exchange transfusions are associated with some risk and certain technical difficulties so that it is impractical for one who is untrained in the method to attempt it Furthermore for its proper application, the physician must be prepared to carry out complete antepartum blood tests including Rh Hr blood typing of the parents siblings, and at times other members of the family to determine the father's zygosity Titration of the Rh anti body in the mother at intervals during preg nancy is also necessary in order to predict with any degree of certainty whether the fetus will be erythroblastotic This again,

involves technical procedures which necessitate training and experience

Often there arises the question of terminating *the pregnancy in an Rh incompatible* mating Certainly, prematurity is an additional handicap to an erythroblastotic infant However, if the father is known to be an Rh homozygous individual and the mother has had previous erythroblastotic babies, premature delivery should be seriously considered, *especially if the maternal anti Rh iso* antibody titer has risen sharply during the latter part of pregnancy In such an event, replacement transfusion by a trained individual should be done immediately after delivery

Finally some general considerations should be mentioned An erythroblastotic baby should not be breast fed, for maternal colostrum and milk contain anti Rh iso antibodies The hemorrhagic tendency exhibited by some of these infants is an indication of profound liver and endothelial damage resulting from anoxemia and the end products of hemolysis As a result, therapy directed toward the prevention of hemolysis and anoxemia is the best approach, and this is accomplished most satisfactorily by the replacement transfusion When hemorrhage does occur, however the frequent administration of vitamin K, and the use of fresh blood for transfusion may be extremely valuable After any transfusion or replacement *transfusion therapy, two to four parenteral*

use of oxygen, parenteral electrolytes glucose, and fluid may be of value as supportive measures depending on the complications which may arise during the infant's first days of life

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SPLENIC ANEMIA

The term splenic anemia has been abandoned by hematologists since the syndromes formerly included in this classification, have been reclassified more specifically on either physiologic or morphologic grounds Congenital hemolytic anemia sickle cell anemia and Cooley's anemia (see p 484) were formerly included in this group as were erythroblastosis fetalis (see p 485) and von Jaksch's anemia The latter term is no longer used since it included various syndromes which have now been classified into one of the more clearly defined groups

The conditions discussed here under the heading of splenic anemia are an unrelated group of diseases associated with anemia and splenomegaly, which is all that they have in common

Primary splenic panhematopenia (Wiseman and Doan) is a syndrome in which neutropenia is the outstanding feature, in the experience of the writers Varying degrees of anemia and thrombocytopenia are also present Removal of the enlarged spleen is usually curative although relapses may occur

Banti's syndrome is characterized by anemia, leukopenia, thrombocytopenia splenomegaly, and cirrhosis of the spleen and liver The clinical diagnosis is difficult to establish and it has been our experience that it is more often arrived at by ruling out other diseases capable of producing the clinical and laboratory findings Splenectomy has been considered to be beneficial in some cases, with or without vascular anastomoses In our cases such operative procedures have provided no benefit, possibly because the diagnosis was established too late Vascular anastomoses have been followed by extensive and sometimes fatal thromboses

The disease finally progresses to the stage of advanced cirrhosis Esophageal varices may bleed profusely necessitating repeated blood transfusions Ascites and edema are treated in the usual manner with paracentesis and diuretics as indicated

Another group of diseases can be included under the heading of splenic anemias since, while the anemia is only one manifestation they enter into the differential diagnosis of any patient with anemia and splenomegaly This is the group of lipoid and nonlipoid reticulo endothelioses including Gaucher's disease Niemann Pick disease, Hand Christian Schuller disease, and Letterer Siwe disease All of these may be associated with anemia, leukopenia thrombocytopenia, and splenomegaly In addition, hepatomegaly and lymphadenopathy may be present There is no effective treatment for these diseases

Splenectomy is even thought to accelerate the course of the disease in some instances although it may be justified in rare instances if the large spleen is causing mechanical difficulties Blood transfusions should be given as dictated by the degree of the anemia Radiation therapy (roentgen ray or radioactive phosphorus) has produced temporary *improvement in some cases but such im*provement is slight and often absent

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AGRANULOCYTOSIS

Agranulocytosis is usually seen following therapy with certain drugs in patients who probably have or have developed sensitivity to the drug in question At this time thiouracil and to a lesser extent propyl thiouracil and related compounds are among the chief offenders Any sulfonamide drug can probably induce the disease although sulfanilamide and sulfapyridine are much more likely to do so than sulfathiazole sulfadiazine or sulfamerazine Aminopyrine was a notoriously common cause of agranulocytosis until the danger was recognized and its widespread use was controlled A variety of

sensitized individual

Clinically the various infections particularly ulcerative lesions of the oral mucous membranes which develop as a result of the severe neutropenia are the outstanding *features of the disease Furthermore it is* now recognized that death results from the infections including pneumonia If death from sepsis can be prevented the granulocytes eventually reappear in the bone marrow and blood and recovery is complete

muscularly every 3 hours if the ordinary aqueous preparations are used or 300 000 units of one of the longer acting preparations at 24 hour intervals Sulfadiazine or sulfamerazine may be similarly effective if it is certain that they were not concerned in the production of the disease in any given patient. Penicillin however is safer and fully as effective and should be used in preference to the sulfonamides

Except for general symptomatic therapy other treatment than administration of penicillin is unnecessary and probably ineffective *The most widely used preparation has* been pentnucleotide in intramuscular doses *of 10 ml four times a day After several years* of observation however it is generally believed that this material produces little if any benefit in addition to which it is painful in the doses used and may produce undesirable systemic reactions

Other materials which have been used in the treatment of agranulocytosis include extract of yellow bone marrow other bone marrow extracts liver extract pteroylglutamic (folic) acid various vitamins blood transfusions and "stimulating" doses of roentgen rays There is no satisfactory evidence that any of these are beneficial and the fact that so many different methods of *treatment have been recommended is a re*flection of the lack of utility of any one of them

With the use of penicillin the mortality rate which in untreated cases exceeded 50 per cent has been reduced to almost nil It appears evident that recovery will eventually occur if the patient is prevented from dying of sepsis in the meantime

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INFECTIOUS MONONUCLEOSIS

Fortunately infectious mononucleosis is a benign self limited disease as there is no specific treatment The acute phase usually runs its course in about 2 weeks time The lingering asthenia which follows however may be most distressing and last for several weeks or months

Since associated Vincent s infection often occurs a saturated solution of sodium perborate or half strength solution of hydrogen peroxide may be useful for cleansing the mouth and throat Penicillin 30 000 units every 3 hours is of value if hemolytic streptococci are found as secondary invaders

none is perhaps quite as important as rest during the active phase of the illness As with infectious hepatitis recrudescence of the disease is likely to occur if too early ambulation or return to full activity is attempted

Convalescent blood or serum has been recommended as of value but these substances usually can be obtained only at the height of an epidemic

Opinion varies as to how strict the isolation of these patients should be During epidemics in susceptible communities reasonable precautions should be taken with excreta utensils and patient contacts for approximately 2 weeks In sporadic cases no special precautions are needed When death intervenes as it occasionally does it is usually due to some complication such as spontaneous rupture of the spleen When splenic rupture occurs immediate surgical intervention is mandatory

Death also has resulted from respiratory paralysis associated with a Guillain Barré syndrome edema of the glottis and supervening infection

Thrombocytopenic purpura occasionally occurs as a complication of infectious mononucleosis In most instances it disappears spontaneously during convalescence However in one instance splenectomy was successfully performed

Hepatitis which frequently occurs with infectious mononucleosis must be treated with prolonged bed rest until the liver function returns to normal In all cases of mononucleosis the liver function should be studied

EDWIN D BAYRD

REFERENCE

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THE LEUKEMIAS

Acute Leukemia Acute leukemia a disease of unknown etiology progresses rapidly with few exceptions to a fatal termination No cure is known In the past treatment has been entirely palliative General supportive measures and transfusions have been the mainstay of treatment Irradiation in most cases is contraindicated but in exceptional cases in which leukemic tumors are encroaching on or interfering with the function of vital organs roentgen therapy in light dosage may be given The administration of radioisotopes such as radiophosphorus is largely ineffectual although some investigators have maintained that the survival times of patients can sometimes be slightly prolonged with this form of treatment

While a cure for acute leukemia remains unknown hope that the disease eventually might be controlled has been kindled recently by the work of Farber and his associates Farber observed that the leukemic process was intensified or accelerated in children who were treated with pteroylglutamic acid (folic acid) He suggested that chemical compounds which were biologically antagonistic to pteroylglutamic acid might inhibit the leukemic process Several so-called antagonists to folic acid have been studied the most effective of which appear to be aminopterin (4 aminopteroylglutamic acid) amethopterin (4 aminomethylpteroylglutamic acid) and amino-an fol (4 amino pteroylaspartic acid) Impressive remissions have been obtained with these substances the incidence of remissions being greater in children than in adults

The mode of action of the antagonists to folic acid in leukemia is not as yet known Normal as well as leukemic tissues are affected but the growth of young rapidly growing cells is impaired more seriously than that of more mature slowly growing cells

The administration of antagonists of folic acid to patients having acute leukemia is followed in most cases by a gradual or rapid reduction in the leukocyte count and a diminution in the number of immature leukemic cells in both the blood and the bone marrow Weakness often profound soreness of the tongue or mucous membranes of the mouth and throat not infrequently followed by ulceration diarrhea and excessive loss of hair may develop any time during the first few weeks of therapy Remissions which may be partial or complete occur most frequently after a month or more of treatment

Antagonists of folic acid are administered intramuscularly Recommended daily dosages are as follows

Dose	*Children*	*Adults*
Aminopterin	0 5 to 1 0 mg	0 5 to 2 0 mg
Amethopterin	3 0 to 5 0 mg	5 0 to 10 0 mg
Amino an fol	25 0 to 50 0 mg	25 0 to 75 0 mg

The size of the individual dose should be gauged by the age weight and physical condition of the patient Since the range between a therapeutic and a toxic dose is negligible it is usually necessary to induce toxic manifestations in order to obtain the desired clinical result However if ulcerative stomatitis diarrhea acute bleeding or an unusually rapid fall in the leukocyte count occurs the administration of antagonists of folic acid *immediately should be stopped* until the cause of the complication has been determined If complications do not develop treatment may be carried on without interruption for weeks or months During remissions the administration of antagonists may be continued in slightly smaller doses than before

All of the antagonists of folic acid studied are toxic The most important toxic manifestations are stomatitis diarrhea ulcerative lesions at any site in or throughout the gastro intestinal tract gastro intestinal hemorrhage which may be massive and severe hypoplasia or aplasia of the bone marrow Toxic manifestations cannot be reversed readily by the administration of pteroylglutamic (folic) acid or liver extract The most effective remedy is the immediate withdrawal of the drug for 4 to 7 or more days

Information concerning the incidence and duration of remissions is as yet incomplete Stickney Mills and their associates at the Mayo Clinic have treated 21 children and 33 adults Among the children 10 had remissions those of 5 were fairly complete These lasted from 1½ to 4 months Eighteen of the 21 children now are dead Among the adults, the incidence of remissions was only approximately 18 per cent The duration of remissions however was similar to that observed in children

Some evidence suggests that acute lymphocytic leukemia responds more favorably to treatment with antagonists of folic acid than acute granulocytic or acute monocytic leukemia does Recently Doan and his associates have suggested that ethyl carbamate (urethane) be employed in the treatment of acute granulocytic leukemia and nitrogen mustard in the treatment of acute monocytic leukemia They reserved the antagonists of folic acid for acute lymphocytic leukemia This matter however requires further study before a final decision can be made

Chronic Leukemia Chronic Granulocytic Leukemia While the average duration of life of patients having either chronic granulocytic or chronic lymphocytic leukemia is approximately 3 years there is marked variation in individual cases and patients are known to have lived 15 years or longer There are as yet no conclusive statistical data that treatment by any of the methods available at present significantly prolongs the lives of leukemic patients However treatment during the earlier stages of the disease almost always alleviates distressing symptoms and in cases in which essentially complete remissions can be induced there may be a return to a sense of normal well being thus permitting these patients to lead normal and useful lives In the later stages the disease is more difficult to control and eventually death occurs despite treatment

Roentgen Therapy Roentgen rays have been used in the treatment of leukemia since early in this century Many different tech

nics have been described which utilize low or high voltage local irradiation over the spleen lymph nodes viscera with leukemic infiltrations or localized leukemic tumors irradiation of the bones or of the whole body The choice of technic depends largely on the facilities available to the roentgen therapist Since treatment with low voltage to the spleen induces remissions in most cases it has been the practice at the Mayo Clinic to administer the smallest effective dose in the shortest possible time thereby

rays

The indications for treatment are a rapidly rising leukocyte count or an increase in im mature forms the development or presence of anemia pressure symptoms progressive loss of weight evidence of leukemic infiltra tion of vital organs and pain resulting from leukemic invasion Unless unduly high an increased leukocyte count alone is not an indication for treatment Leukemic patients with leukocyte counts in the neighborhood of 100 000 cells per cubic millimeter or more may show no signs of progression of the disease for months or even, occasionally for longer periods

Roentgen irradiation may be given daily or at less frequent intervals If a daily sched ule is being utilized leukocyte counts should be made each morning before the patient is treated Treatment should be stopped alto-gether or interrupted temporarily if the leukocyte count falls rapidly if irradiation sickness becomes severe and dehydration develops as a result of frequent vomiting if the condition of the patient suddenly be comes worse or if complications such as severe bleeding occur If treatment does not have to be interrupted for one of the above reasons it is continued until the de sired result is obtained that is until marked diminution in the leukocyte count with re duction in the size of the spleen or lymph nodes or both occurs

No specific rules can be made as to just when treatment should be discontinued but it should be remembered that a significant drop in the leukocyte count occurs during the first 2 to 3 weeks after cessation of therapy For example, if the leukocyte count has fallen slowly and treatment is terminated when the count approaches 30 000 cells per cubic millimeter of blood a drop to 10 000 cells or even less not infrequently occurs after treatment is stopped On the other hand in cases in which the fall in leukocytes is rapid the continued administration of roentgen therapy until the leukocyte count has reached 30 000 cells per cubic millimeter would be extremely hazardous because an extreme degree of leukopenia might be in duced In such instances it is advisable to terminate treatment when the leukocyte count has fallen to 60 000 or 75 000 cells per cubic millimeter

dividuals with markedly elevated counts but when necessary it may be carried out safely if proper precautions are taken and the patient is watched carefully However,

myelosclerosis (agnogenic myeloid meta plasia), which may simulate closely leuko-penic myelogenous leukemia

During periods of remission patients should be followed carefully The remission may last from a few weeks to many months Recurrence of symptoms progressive in crease in the leukocyte count an increase in the number of immature forms in the blood and development of anemia or an increase

tered is an effective and valuable means for controlling this disease for long periods Eventually however refractoriness to irradi ation develops Some of the patients may re spond temporarily at least to other forms of therapy such as the administration of urethane In a fairly high proportion of cases acute leukemia develops as a terminal event Treatment with roentgen rays at this stage of the disease is ineffectual

The principal disadvantages of roentgen therapy are (1) irradiation sickness (2) the time required for treatment, and (3) the cost of repeated courses of therapy There is some evidence to suggest that irradiation sickness may be prevented or mitigated

fairly high proportion of cases by the intra venous injection of 100 to 200 mg of pyridoxine hydrochloride a half hour before *roentgen treatment* is administered (Wells and Popp) Recently, dramamine (B dimethylamino ethylbenzohydryl ether 8 chloro theophyllinate) 50 mg *three times daily,* also has been found to be beneficial (Beeler et al) Proper ventilation of rooms when treatment is given, lengthening of the interval between treatments for patients who have had irradiation previously, and the administration of a sedative, such as a barbiturate, an hour or two before treatment are also helpful If irradiation sickness accompanied by frequent vomiting develops despite these precautions, dehydration should be prevented by *parenteral administration of fluids* The intravenous administration of solutions of *glucose is particularly helpful*

Radium Radium has been used successfully in the treatment of chronic leukemia but it does not appear to have any particular advantage over roentgen irradiation The mode of action the indications and contra indications and the measures utilized to prevent overtreatment are essentially the same

Since then, this form of therapy has been used *extensively* at a number of institutions in this country Ample data concerning the immediate results of administration of the isotope have been reported but information concerning the long range effects is incomplete Recently, however, Lawrence and his co workers have presented evidence indicating that the comfortable life of leukemic patients treated with radioactive phosphorus is prolonged

The radioactive phosphorus originally used by Lawrence and others was prepared by bombarding ordinary red phosphorus (P^{31}) with deuterons in the cyclotron At present, radiophosphorus is made from neutron bombardment of sulfur in the atomic pile The radiophosphorus in both cases is the same Carrier free radiophosphorus, brought to isotonicity by the addition of solution of sodium chloride, is now available in which *essentially* all of the phosphate present is radioactive The beta ray activity of the solution is standardized in terms of microcurie radium equivalents against a uranium beta ray standard Following sterilization, this solution can be administered intravenously or given orally

The half life, absorption excretion and *distribution of radioactive phosphorus* are discussed in the section dealing with the treatment of polycythemia vera Calculation of dosage is based on equivalent roentgens of whole body radiation delivered by the quantity of radioactive phosphorus administered The formulas devised by Tobias facilitate the conversion of doses of radioactive phosphorus in millicuries to roentgen equivalents For intravenous administration the total dose in roentgen equivalent physical* *is*

$$N \times T \times 1.44 \times 0.52 \times \frac{40}{\textit{weight in grams}}$$

where N represents microcuries T signifies half life the figure 1 44 is an expression obtained from the integration of the dose over infinite time, the factor 0 52 relates to the rate of absorption and excretion, and the figure 40 is the initial dose rate (derived from the fact that 1 millicurie of radioactive phosphorus per gram of tissue will give 40 roentgens of irradiation in a period of 24 *hours*) *For oral administration, the formula* is the same except for a change in the factor relating to rate of absorption and excretion This now becomes 0 38

In order to afford prolonged and fairly constant irradiation of leukemic tissues radioactive phosphorus is administered either intravenously or orally, once or twice a week until the desired effect is obtained Thus, the method of administration differs from that *employed in the treatment of* polycythemia vera As a general rule, initial doses of from 1 to 3 mc are given Thereafter, smaller amounts, usually from 0 5 to 1 5 mc are administered, the size of the individual dose depending in part on frequency of administration and in part on the hematopoietic and clinical response obtained As the leukocyte count diminishes, it is advisable gradually to reduce each dose of *radioactive phosphorus* Since there is considerable individual variation in the response

* One roentgen equivalent physical (rep) is the dose of ionizing radiation which will deliver 83 ergs per gram

of patients to this form of therapy no hard and fast rules can be given However careful hematologic observation is essential Leukocyte erythrocyte and platelet counts should be obtained before each injection of the isotope

The total quantity of radioactive phosphorus required to induce remissions is extremely variable In some cases 4 0 or 5 0 mc administered intravenously over a period of 1 or 2 weeks may be sufficient to produce the desired result in others total doses of 25 or 30 mc given over periods of many weeks may be required

Treatment with radioactive phosphorus

companied by diminution in the size of the spleen and lymph nodes occurs The leukocyte count gradually falls and the number of immature cells in the peripheral blood is reduced Concomitantly if anemia is present prior to treatment there is a gradual increase in the erythrocyte count not infrequently to a normal value

The duration of remissions is variable lasting from a few months to more than a year When relapse occurs remissions can again be induced by giving additional courses

The principal advantages of treatment with radioactive phosphorus appear to be the ease with which generalized irradiation

bility that the incidence of an acute leukemic phase as a terminal event is higher than in patients treated solely by means of roentgen irradiation The latter however appears to be offset by the fact that a comfortable and useful life is probably longer than among patients treated with roentgen rays

Urethane (Ethyl Carbamate) Urethane was introduced as a therapeutic agent for leukemia by Paterson Haddow Ap Thomas and Watkinson in 1946 The administration of this agent in selected cases produces a fall in the leukocyte count reduction in the number of immature forms in the blood stream diminution in the size of the spleen and symptomatic improvement As the leukocyte count falls the erythrocyte count and values for hemoglobin if below normal prior to treatment frequently increase and in many cases return to normal

Although urethane may be administered intramuscularly or intravenously it is most easily given by mouth Moreover the intravenous route is not without danger Paterson and associates originally prescribed urethane in a solution of chloroform and syrup of orange but this mixture no longer is utilized because of the possible deleterious effects of chloroform Gelatin capsules containing 0 5 gm or 0 3 gm and 0 5 gm enteric coated capsules or tablets as well as a solution in the form of an elixir now are available for

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pleasant side effects such as anorexia nausea and vomiting Experience has shown that as small a dose as will produce a gradual reduction in the leukocyte count is most satisfactory although a month or more may be required to produce the desired clinical results As the leukocyte count falls the daily dose of urethane should be diminished This necessitates blood examinations twice or thrice a week until the leukocyte count approaches normal levels Once values approximating normal have been reached the patient should be placed on maintenance doses of from 0 5 to 1 5 gm daily If administration of the drug is stopped the leukocyte count increases rapidly and clinical manifestations of relapse develop During periods of maintenance therapy examinations of blood should be performed every week or two because adjustments in dosage not infrequently have to be made Since urethane does not have a cumulative action it may be administered continuously for long periods

[illegible] administration of the drug have been reported. However complications of this type appear to be rare

Symptoms of intolerance to the drug are anorexia nausea vomiting and drowsiness These symptoms are encountered infrequently in patients receiving moderate doses of urethane but they are common in those

receiving larger doses (3 0 to 5 0 gm daily) If sufficiently distressing the administration of urethane should be discontinued and some other form of therapy instituted

Nitrogen Mustards These compounds have been used principally for the treatment of the malignant lymphomas However they have been studied rather extensively for their potential value as therapeutic agents in leukemia as well The comprehensive report of Burchenal and associates showed that methyl *bis* (β chlorethyl) amine and *tris* (β chlorethyl) amine produced results in chronic granulocytic leukemia similar to those obtained with roentgen irradiation or with radioactive phosphorus As a rule however the remissions were somewhat shorter than those noted after irradiation In chronic lymphocytic leukemia the response to treatment was satisfactory among patients in an early stage of the disease but poor among patients with far advanced disease In acute leukemia treatment with nitrogen mustard proved to be of little value although temporary symptomatic relief was observed in some cases

The pharmacology mode of action method of administration dosage of the nitrogen mustards and the complications arising from this form of therapy are discussed in the section on Hodgkin s disease and allied disorders

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Toxic manifestations frequently occur These include anorexia nausea vomiting restlessness insomnia loss of weight diarrhea and with prolonged treatment pig*mentation and keratosis of the skin* and peripheral neuritis Because of the toxicity of the drug roentgen irradiation radioactive phosphorus or urethane therapy is to be preferred However the administration of Fowler s solution to patients who have become refractory to roentgen treatment sometimes results in temporary improvement and may therefore be worth a trial

Other Agents Benzene at one time was widely advocated as a useful agent for treating chronic granulocytic leukemia Initial doses of 3 0 gm daily were recommended the daily dose gradually being increased to 4 0 or 5 0 gm The drug then was withdrawn gradually as the leukocyte count fell This method now is rarely employed in this country

Other methods of treatment such as the administration of various organ extracts (spleen) antimony and aminopyrine have not proved to be of value

Splenectomy This procedure is contraindicated except in rare instances in which hemolytic anemia is superimposed on the basic leukemic process In such cases splenectomy may be followed by a lessening of or cessation of excessive hemolysis and thus the patient s life may be prolonged

General Measures There is little or no need to restrict the activities of leukemic patients during periods of remission However *during periods of relapse* some restriction is advisable Rest in bed is desirable in patients with fever or far advanced leukemia with an associated severe anemia

A well balanced nutritious isocaloric diet will meet the requirements of most patients

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Severe infections are particularly likely to develop in cases of leukemia especially in the late stages of the disease or in those in

which leukopenia is present Ulcerative lesions in the mouth or throat not infrequently occur and may be followed by the development of bacteremia Oral hygiene therefore is important Thorough cleansing of the mouth after each meal with an alkaline mouth wash or a mild antiseptic solution such as hydrogen peroxide is desirable and a soft toothbrush should be used for brushing the teeth in order to minimize the risk of injuring the mucous membranes In the presence of serious infections antibiotic agents or the sulfonamides or both are especially useful For ulcerations of the skin resulting from necrosis of localized leukemic tumors the local application of sulfathiazole powder will effectively control secondary infection in the ulcerated area in most cases and not infrequently will be followed by healing

Treatment of the anemia associated with chronic leukemia may present a difficult problem for the physician if the anemia persists after the leukocyte count has been reduced by roentgen irradiation or other measures In such cases the persistence of anemia implies the existence of far advanced disease and the administration of iron extracts of liver folic acid or vitamin B_{12} is ineffectual The judicious use of properly spaced transfusions of blood is beneficial although the benefit derived from this procedure is only temporary Sturgis advocated the use of fresh blood for patients with thrombocytopenia or ulcerative lesions of the mucous membranes but preserved or bank blood is satisfactory for use in cases in which these complications do not occur

CHRONIC LYMPHOCYTIC LEUKEMIA *Roentgen Irradiation* This method of treatment remains the treatment of choice for chronic lymphocytic leukemia Remissions often of long duration can be induced with it and with repeated courses of treatment the disease may be controlled and a comfortable life afforded for several years The indications for treatment are (1) marked adenopathy of the peripheral lymph nodes (2) pressure symptoms resulting from enlargement of mediastinal or intra abdominal lymph nodes from an enormously enlarged spleen or from localized leukemic growths in vital areas and (3) a high leukocyte count with an associated anemia On the other hand if there is no significant adenopathy enlargement of the spleen or anemia it is usually advisable to withhold treatment until one or more of these manifestations de

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Radiophosphorus In general roentgen irradiation is to be preferred to treatment with radioactive phosphorus in chronic lymphocytic leukemia for two reasons (1) Roentgen therapy affords maximal irradiation of lymphoid tissue with only a relatively minor inhibitory effect on hematopoiesis in the bone marrow (2) the administration of radioactive phosphorus results in greater irradiation of the marrow than of lymphoid tissue where maximal irradiation actually is desired Consequently the incidence of thrombocytopenia and anemia is higher among patients treated with radioactive phosphorus than among those receiving roentgen irradiation The principal indication for treatment with radioactive phosphorus in chronic lymphocytic leukemia is evidence of massive leukemic involvement of the bone marrow on sternal aspiration together with associated anemia In cases of this type administration of the isotope not infrequently induces remissions and results in improvement of the anemia The dosage and method of administration are similar to those employed in chronic granulocytic leukemia

Urethane The results of the administration of urethane to patients having chronic lymphocytic leukemia are more variable than those obtained in chronic granulocytic leukemia In cases in which the response is favorable the leukocyte count falls to values approaching normal the differential count approaches a more normal pattern diminution in the size of enlarged lymph nodes and spleen occurs and values for hemoglobin and erythrocytes frequently rise In general however roentgen irradiation produces more uniformly good results and therefore is to be preferred to urethane

Nitrogen Mustards See discussion in section on Hodgkin s Disease and Allied Disorders

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lied disorders

Arsenicals Arsenic in the form of Fowler's solution (solution of potassium arsenite U S P), first used as early as 1865 fell into disuse after the introduction of roentgen irradiation until the work of Forkner and Scott in 1931 revived interest in it Beneficial results can be obtained with it in some cases, but it is more toxic than urethane The method described by Forkner and Scott is as follows Five minims (0 3 cc) diluted in fruit juice are administered with or immediately after meals three times daily for 2 or 3 days Then the dose is increased by 3 minims daily (to 6 minims three times a day, then to 7 minims three times a day and so on) until 10 minims three times a day are being given Thereafter, the dose is increased by 1 minim daily until the desired effect is obtained or until symptoms of toxemia develop In either event, treatment is suspended for 2 to 5 days then resumed by reducing the dose from the maximum by 1 minim daily until a maintenance dosage of 5 to 8 minims three times a day is attained Maintenance therapy may be continued for long periods but adjustments in dosage may be required from time to time

Toxic manifestations frequently occur These include anorexia, nausea, vomiting restlessness, insomnia, loss of weight, diarrhea, and with prolonged treatment, pigmentation and keratosis of the skin and peripheral neuritis Because of the toxicity of the drug, roentgen irradiation, radioactive phosphorus, or urethane therapy is to be preferred However, the administration of Fowler's solution to patients who have become refractory to roentgen treatment sometimes results in temporary improvement and may, therefore, be worth a trial

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General Measures There is little or no need to restrict the activities of leukemic patients during periods of remission However, during periods of relapse some restriction is advisable Rest in bed is desirable in patients with fever or far advanced leukemia with an associated severe anemia

A well balanced, nutritious isocaloric diet will meet the requirements of most patients during periods of remission However, a high caloric diet with nourishment between meals is advisable for patients with an increased basal metabolic rate or with fever

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Nitrogen Mustards See discussion in section on Hodgkin s Disease and Allied Disorders

General Measures These are essentially the same as those outlined for chronic granulocytic leukemia

CHRONIC LEUKEMIC RETICULO ENDOTHELIOSIS This disease is not infrequently consistent with a comparatively long life, some patients living for 10 years or more In our experience, roentgen irradiation and properly spaced blood transfusions give the best results However, roentgen irradiation should be administered in courses as sparingly as possible, and only if pressure symptoms from an enormously enlarged spleen become especially troublesome or if the leukocyte count is unduly high Anemia is not an indication for the administration of roentgen therapy Treatment with radioactive phosphorus or the nitrogen mustards is contraindicated because of the risk of seriously inhibiting hematopoiesis, resulting in the development or intensification of leukopenia, anemia, and thrombocytopenia Thrombocytopenia is a particularly serious complication *because of the danger of fatal hemorrhage*

BYRON E HALL

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HODGKIN'S DISEASE AND ALLIED DISORDERS

The classification of this group of diseases has been a controversial subject for many years None of the proposed classifications have found universal acceptance However despite certain shortcomings, we have found the classification made by Jackson and Parker particularly useful Fortunately, from the standpoint of therapy, the entire group may be considered together This discussion therefore, will embrace the treatment of Hodgkin's disease, lymphosarcoma, lymphocytoma, lymphoblastoma (used in the strict sense), reticulum cell sarcoma, and giant follicle lymphoma (giant follicular hyperplasia)

While it is generally conceded that active treatment affords a more comfortable life, few statistics are available concerning survival rates in treated and untreated groups of patients Stout s report, therefore, is significant Survival rates are presented from a study of 119 treated and 51 untreated patients with lymphosarcoma Five years after the diagnosis was made 23 5 per cent of the treated group survived, and 15 per cent were symptom free, whereas only 2 per cent of the untreated group survived and *none* [illegible] after the diag [illegible]

free of symptoms, whereas none of the un

treated group were alive Thus, it would appear that active treatment does prolong life, at least in cases of lymphosarcoma

amenable to surgical treatment However,

cally early lymphoma followed by prophylactic external irradiation have shown 5 year survival rates of approximately 25 per cent of patients For lymphosarcoma of the head and neck, the results have been even better as Catlin reported a 5 year survival rate of 52 per cent Hellwig's statistics also are of

tion

While the results of radical surgical removal are not as yet convincingly superior to intensive irradiation nevertheless this procedure does offer a chance of cure Therefore, in carefully selected cases, extirpative surgery should receive serious consideration

Roentgen Irradiation and Radium Roentgen irradiation is the mainstay of treatment for the malignant lymphomas It is used in treating either localized or generalized disease, high voltage being employed when deep penetration is desired Radium now is used infrequently, although it is useful in the treatment of localized, superficial lesions

Inasmuch as the clinical manifestations in this group of diseases vary tremendously, it is particularly important that treatment be individualized Modifications in procedure must be adapted to the stage of the disease and the accessibility of the lesions Hare

disease, these results are comparable to those obtained from local extirpation followed by irradiation It should be remembered, however, that obliterative irradiation has undesirable late effects, such as fibrosis, telangiectasia, and irradiation dermatitis

Craver, in a discussion of dosage for adequate treatment of early lesions, was of the opinion that the maximal dose tolerated by the skin overlying the lesion should be given in fractional increments

For generalized disease, various areas are treated in succession unless irradiation of the whole body is employed During periods of treatment, the condition of the patient and the effect on the blood and tissues must be watched If the patient is receiving treatment every day or every second day, leukocyte counts should be obtained preceding each treatment Irradiation is continued until all areas have been treated, unless leukopenia of severe degree or irradiation sickness with vomiting and dehydration develops If either of the latter occurs, treatment should be discontinued temporarily or for a longer period, depending on the condition of the patient Once remission has been induced, additional roentgen treatment should be withheld until definite signs of relapse occur, thus allowing for maximal recovery of normal tissues between courses of treatment

Far advanced disease and large tumor masses do not respond as readily to irradiation as early or moderately advanced disease, or small, recently enlarged groups of lymph nodes Under these circumstances, heavier irradiation will be required However, after repeated courses of treatment, refractoriness to roentgen irradiation eventually develops When this is encountered, the administration of one of the nitrogen mustards may result in temporary improvement

Although the remissions induced by the nitrogen mustards rarely are complete and seldom last more than 6 to 12 weeks, repeated courses can be given each time a relapse occurs Thus, the lives of many of these patients can be prolonged, and in some instances after intervals of several months roentgen irradiation may again become effective

The results of irradiation of the whole

expected

Radiophosphorus The use of this isotope is contraindicated in all cases of early and

in most cases of advanced malignant lymphoma, except possibly cases of far advanced disease with extensive involvement of the bone marrow. *The administration of radioactive phosphorus is complicated by the development of thrombocytopenia and leukopenia, often of severe degree, long before maximal irradiation of diseased lymphoid tissue is achieved.*

Nitrogen Mustards. These compounds are halogenated alkyl or β chlorethyl amines all having the same fundamental chemical structure. When they are dissolved in polar solvents ethylenammonium derivatives are produced by intramolecular ionization, resulting in the liberation of a cyclic onium cation which has an action on cells and tissues similar to that produced by irradiation. These derivatives, and not the nitrogen mustards themselves, are cytotoxic. The two compounds most extensively studied so far are methyl *bis* (β chlorethyl) amine hydrochloride (HN_2) and *tris* (β-chlorethyl) amine hydrochloride (HN_3). Their mode of action is characterized by inhibition or inactivation of enzyme systems, inhibition of mitosis, and induction of chromosomal abnormalities.

The degree of response is roughly proportional to the dose employed, large doses affect virtually every cell in the body. However, rapidly growing cells, whether normal or neoplastic, are more susceptible to the cytotoxic effect of these compounds than slowly growing cells. Hematopoietic tissues are especially susceptible.

The action of the nitrogen mustards on the hematopoietic tissues is reflected by the development of leukopenia, associated at first with lymphopenia, and later with granulopenia. In some cases, thrombocytopenia and anemia also may develop. Lymphocytopenia may be apparent within 24 hours after the first injection of the drug and becomes progressively *more severe for 8 to 10 days.* Granulocytopenia develops gradually over a period of 2 to 3 weeks after a course of treatment, and the thrombocytopenia *may be noted* at this time also. Thereafter, blood counts gradually return to normal.

Nitrogen mustard compounds are stable in *dry form,* but unstable in aqueous solution. Fresh solutions, therefore, must be used. These are made by adding 10 cc. of sterile isotonic solution of sodium chloride to sterile glass tubes or bottles, each containing 10 *micrograms of the dry salt.* Immediate injection of the fresh solution is important. Only the intravenous route of administration is employed. Considerable care should be *taken to prevent these solutions from coming* into direct contact with the skin or from escaping from the vein into the surrounding tissues.

The standard single dose now generally employed for the methyl *bis* and *tris* (β chlorethyl) amine compounds is 0.1 mg. per kilogram of body weight. A course of treatment *consists in most instances of three to* six injections of either compound every day or every second day, the total dose thus varying from 0.3 to 0.6 mg. per kilogram of body weight. Although treatment must be individualized, most patients will tolerate well a total dose of 0.4 mg. per kilogram of body weight. While the total amount to be given for one course of treatment can be administered either in one or in two injections, complications, especially thrombophlebitis in the vein used for the injection are more apt to occur when it is given in this manner. For doses of 0.1 mg. per kilogram of body weight, the material may be injected directly into a vein, but for larger doses the incidence of thrombophlebitis can be lessened if the drug is injected into the rubber tubing of an intravenous apparatus during the course of an infusion of saline or glucose solution which is being delivered at a relatively rapid rate.

In three groups of cases of malignant lymphoma treatment with the nitrogen mustards appears to be specifically indicated. These are (1) *cases of far advanced disease* which has become refractory to irradiation therapy, (2) cases of acute disease failing to respond to roentgen irradiation and (3) *cases of widespread systemic* disease with extensive visceral involvement. The nitrogen mustards should not be used for early localized lymphoma or for moderately advanced systemic disease still responding well to roentgen therapy. Their use for giant follicle

dition is relatively benign and the risk of treatment outweighs the hazards of the disease itself

The nitrogen mustards are potentially dangerous drugs Hence before using the

be both local and systemic If extravasation of nitrogen mustard compounds occurs during injection pain followed by a tender indurated swelling occurs at the site of injection and the latter resolves slowly Early systemic effects are nausea and vomiting which occur in a high proportion of cases beginning 1 to 3 hours after injection and lasting several hours However not infrequently the nausea and vomiting subside after the first or second injection during a single course of treatment Anorexia is less frequent and usually is transient Diarrhea rarely occurs

Delayed reactions are thrombophlebitis and thrombosis in the vessel used for the injection and widespread severe destruction of hematopoietic tissues Hypoplasia or aplasia of the marrow may develop and the resulting thrombocytopenia may be accompanied by hemorrhagic phenomena Death from cerebral hemorrhage occasionally occurs Damage to organs such as the liver has not been demonstrated by special function tests (Hellwig)

The results of treatment with the nitrogen mustards appear to be somewhat more favorable in Hodgkin s disease than in some of the other forms of malignant lymphoma Rhoads reported that approximately 70 per cent of the patients treated show objective improvement and 90 per cent subjective improvement There are failures Remissions are of short duration lasting from 1 to 3 months rarely as long as 6 months They can be induced not only once but in many cases many times with subsequent courses of treatment Patients whose condition has become refractory to roentgen irradiation may respond favorably and sometimes dramatically to treatment with this compound Moreover there is now some evidence to show that sensitivity to irradiation may be restored in occasional patients after successive courses of treatment with the nitrogen mustards

are more common severe toxic reactions are more prone to occur and an increasing resistance to successive courses of therapy is more likely to be encountered In mycosis fungoides nitrogen mustard therapy has been found to be a useful adjunct to roentgen irradiation also (Kierland et al Henstell et al)

General Measures These are essentially the same as those outlined for chronic granulocytic leukemia

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POLYCYTHEMIA VERA

Polycythemia vera is a chronic disease with protean manifestations which not infrequently are associated with other disease processes for example gout duodenal ulcer *arterial occlusive disease and so forth* Although no cure is known for it the primary aim of treatment is (1) control of the disease itself and (2) control or alleviation of associated diseases

Control of the primary disease may be accomplished by reducing the total blood volume through (1) withdrawal of blood (*venesection*) (2) destruction of erythrocytes by administration of phenylhydrazine or (3) interference with production of blood by use of roentgen therapy radiophosphorus chemical agents or the administration of a diet low in blood building substances especially iron In selecting what form of treatment to employ, it is advisable to keep in mind the major complications of this disease thrombosis and hemorrhage The increased blood volume erythrocyte and platelet counts and viscosity lead to slowing of blood flow and predispose to thrombosis the principal cause of death The increased blood volume associated with distention of blood vessels often leads to hemorrhage the next most common cause of death Treatment, *therefore should be directed toward the* reduction of those factors which predispose to thrombosis and hemorrhage

Venesection Venesection long employed as a method for treating polycythemia vera is preferred by many *clinicians to other* technical difficulties of withdrawing blood of increased viscosity and (2) the difficulty of maintaining the patient in satisfactory *remission over long periods of time*

Venesections on polycythemic patients are facilitated by adherence to a few simple rules Clotting of blood in the needle is less likely to occur if a large gauge needle (15 gauge) and suction (vacuum bottle) are employed Of even greater importance is the introduction of the needle into the vein against the direction of blood flow so that *a direct flow of blood from the vein through* the needle occurs Cutting down on veins for the purpose of inserting the needle should be avoided except in emergencies because the subsequent development of scar tissue frequently precludes the use of these veins for future venesection Quantities of 500 to 700 cc are withdrawn at intervals of 1 or *2 days until the volume of erythrocytes has* been reduced to normal

Maintenance therapy should be instituted after a normal cell volume has been established This consists simply of periodic examinations of blood and the performance of venesections as often as necessary to maintain a normal cell volume The frequency with which venesections should be performed will vary from patient to patient hence the interval between examinations of the blood *must be individualized for each patient* Not infrequently, remissions lasting weeks or months will be noted after a normal volume of erythrocytes has been established *from* the initial series of venesections

Polycythemia vera of mild degree can be controlled by means of venesections alone provided that the patient understands the nature of his illness and the importance of

adequate control Polycythemia vera of severe degree presents a more difficult problem because the individual requiring frequent venesections often becomes discouraged and fails to co operate fully with his physician In cases of this type the utilization of forms of therapy offering the patient hope of remissions of long duration would appear to be justified Dameshek and Henstell advocated the production of a chronic iron deficiency by means of repeated venesections and adherence to a diet low in iron Treatment of polycythemia vera by withdrawal of massive quantities of blood and transfusions of plasma has also been suggested (Widstrom and Swedberg)

Phenylhydrazine The oral administration of phenylhydrazine is effective in controlling polycythemia vera in many but not all cases This drug (C_6H_5 NH NH_2) is prepared from aniline and is related to antipyrine Crystalline phenylhydrazine or acetylphenylhydrazine should be used since liquid phenylhydrazine is unstable Both compounds are equally effective and are generally given in the form of capsules

The action of phenylhydrazine on the blood presumably is hemolytic the degree of hemolysis obtained being proportionate to the dose administered The administration of the drug is followed by neutrophilic leukocytosis decrease in erythrocytes increase in plasma bilirubin reticulocytosis and diminution of the total blood volume If destruction of the blood is sufficiently pronounced nucleated erythrocytes may appear in the circulation

As originally employed phenylhydrazine was utilized to reduce the total blood volume Doses of 0 1 gm were given two or three times daily until evidence of active hemolysis was observed or until a total of 3 0 to 4 0 gm had been administered Since a number of deaths were encountered principally from acute hemolytic anemia or the development of thrombotic phenomena the use of phenylhydrazine as the initial form of treatment was avoided for patients more than 60 years of age for patients confined to bed for patients with advanced arteriosclerosis or visceral disease and for patients who had a history of thrombosis After a normal cell volume had been achieved maintenance therapy consisted of the administration of 0 1 to 0 3 gm of phenylhydrazine each week

Treatment with phenylhydrazine to reduce the blood volume is seldom employed now since restoration of normal blood volume can be accomplished initially far more safely by means of repeated venesections However once the blood volume has been restored to normal as a maintenance measure 0 1 to 0 4 gm weekly can be given to patients who tolerate the drug Ordinarily 0 1 gm of phenylhydrazine is given by mouth three times a day on one day only of each week

The principal disadvantages of maintenance therapy with phenylhydrazine are (1) intolerance of many patients to the drug the most common symptom being nausea and (2) its failure to lower significantly the incidence of thrombotic phenomena

Roentgen Irradiation Of the various forms of roentgen irradiation that have been used total body irradiation ("spray therapy") is the most successful Roentgen therapy to the spleen not only fails to induce remissions but seldom significantly diminishes the size of this organ Irradiation of the bone marrow (systemic treatment of the principal bones containing red marrow) is more effective but the results frequently are transitory Since 1932 when Sgal tzer first reported encouraging results from irradiation of the entire body a number of reports have appeared The report of Richardson and Robbins is impressive Of 28 patients treated over a period of 15 years therapeutic failure was noted in only one instance Remissions lasting from 1 5 to 5 5 years were obtained in a small number of cases from one course of treatment In most cases however multiple courses of treatment were required to control the disease At the end of the period of observation 16 patients were living and 12 had died The survival time in the latter group ranged from 1 5 to 11 years with an average of 5 6 years Four patients in this group died of causes not attributable to the polycythemia The survival time among the patients still living ranged from 1 5 to 9 years with an average of 5 4 years

From the results obtained by Richardson and Robbins and others spray irradiation appears to be an effective method for controlling polycythemia vera The chief disadvantages of the method are (1) the need for

the roentgen therapist to possess special and expensive equipment, (2) the time required for one course of treatment, (3) the discomfort to the patient of roentgen sickness, and (4) the possibility of injurious immediate or long range effects Refractory anemia and acute leukemia developing as a terminal event in polycythemic patients who have received whole body irradiation have been reported Whether roentgen therapy can be incriminated as causing the development of acute leukemia in patients having polycythemia vera is problematic, since this condition, although rare, has been observed as a terminal event in polycythemic patients who had not been treated with irradiation in any form In any case, the occurrence of refractory anemia or acute leukemia is sufficiently unusual that neither of these conditions need be considered a contraindication to the use of spray irradiation in patients having severe or moderately severe polycythemia vera

Radiophosphorus The administration of radioactive phosphorus to patients having polycythemia vera in relapse is highly effective in controlling this disease Remissions, often of long duration can be induced in a high percentage of patients, and the incidence of the major complications of the disease can be reduced materially While the results of treatment are sufficiently impressive to suggest that this method is superior to other methods currently in use, emphasis should be placed on the fact that the long-range effects of introducing radioactive phosphorus into the human body have not been determined The possibility of the development of neoplastic disease, especially acute leukemia, in a small number of patients treated with radioactive phosphorus has been a subject of grave concern Although the incidence of acute leukemia is slightly higher among patients treated with radioactive phosphorus than among those treated by venesections or the administration of phenylhydrazine, the incidence of thrombosis, hemorrhage, and a terminal chronic leukemic picture is significantly less Hence, the hazards ascribed to treatment with radioactive phosphorus appear to be materially less than those associated with uncontrolled or only partially controlled polycythemia However, until the long range effects of treatment with radioactive phosphorus are known, it would seem advisable to restrict this form of treatment to use in those cases in which polycythemia is not easily or well controlled by other means

Radiophosphorus should be administered only by physicians experienced in its use The isotope is distributed under the auspices of the Isotopes Branch of the U S Atomic Energy Commission to properly trained physicians who have available to them requisite laboratory equipment for measurement and handling

Radioactive phosphorus has a half life of 14 3 days It emits only beta rays, which have a maximal range of penetration in tissues of approximately 7 mm, and an average range of penetration of about 2 mm Thus irradiation is confined primarily to those tissues in which radioactive phosphorus is deposited The isotope may be given orally or parenterally When given orally, approximately 75 per cent is absorbed from the gastro intestinal tract (Reinhard et al) Although the amount lost by fecal excretion is not constant, it is generally safe to add 25 per cent to the calculated parenteral dose if one wishes to administer the isotope by mouth

When radioactive phosphorus is administered intravenously, from 5 to 25 per cent of the administered dose is excreted in the urine in the first 4 to 6 days The portion not excreted is deposited in bone marrow, lymph nodes, liver, spleen and later in bone Rapidly growing cells incorporate more radioactive phosphorus than slowly growing tissues Thus, greater amounts of radioactive phosphorus are deposited in rapidly growing leukemic cells than in normal cells Because radioactive phosphorus is deposited primarily in bone marrow and later as phosphate in bone, this isotope is highly effective for irradiating the bone marrow Inhibition of hematopoiesis is thereby accomplished However, the inhibitory effect of radioactive phosphorus on erythropoiesis in patients having polycythemia vera may not be discernible in less than 6 to 8 weeks after the administration of the initial dose The life span of the erythrocyte is in the neighborhood of 90 to 120 days, and since radioactive phosphorus does not destroy erythrocytes several weeks must elapse before erythro

cytes age and are removed from the circulation

The method my colleagues and I employ in treating patients with polycythemia vera in relapse is as follows Daily venesections are performed until the cell volume (hematocrit) has been lowered to 55 per cent or less This is done to diminish the risk of the development of thrombotic phenomena in the interval between the administration of radioactive phosphorus and the period several weeks later when the inhibitory effect of radioactive phosphorus on hematopoiesis becomes manifest Then, a single intravenous injection of from 3 to 7 millicuries of radioactive phosphorus is administered, the size of the initial dose being based on the apparent clinical severity of the disease In most cases, initial doses of from 5 to 6 millicuries are employed The patient is then instructed to have the blood examined at intervals of 4 and 6 weeks, and to return at the end of 8 to 12 weeks for a second injection of radioactive phosphorus if a remission has not been induced Leukocyte and platelet counts, in addition to determination of cell volume and an erythrocyte count, should be made before the administration of the second dose If leukopenia or thrombocytopenia of severe degree has developed the administration of additional radioactive phosphorus should be withheld until the leukocyte or platelet count has returned to values approximating normal If leukopenia or thrombocytopenia of mild or moderate degree is found the size of the second dose should be smaller than the first However in those cases in which neither leukopenia nor thrombocytopenia is encountered the size of the second dose may approximate the first The same plan as that after the first injection is then followed for later injections, a third, fourth, and even a fifth injection may be given at intervals of 2 to 3 months until a remission has been induced

In experience at the Mayo Clinic, radioactive phosphorus therapy is highly successful if proper co operation between patient and physician is established It is important to instruct the patient in the necessity for re examinations of the blood at regular intervals after the initial treatment Remissions may be expected after one injection of radioactive phosphorus among approximately a third of all the patients treated, and after two injections among another third The remaining third may require from three to five injections Remissions may last from 6 months to 6 years, the average in our series of cases was from 18 to 24 months (Hall)

The most common complications encountered as a result of treatment with radioactive phosphorus are the development of leukopenia, thrombocytopenia, and anemia As a rule, these are not serious, and recovery is complete in the course of a few weeks if no further treatment is given Severe hypoplasia of the bone marrow may result from overdosage, or rarely, from the administration of amounts of radioactive phosphorus of therapeutic magnitude When hypoplasia of the marrow is encountered treatment consists of the administration of blood transfusions at periodic intervals until erythropoiesis again becomes active This may require several months

The advantages of radioactive phosphorus therapy are the simplicity of the method, the ease of administration, the absence of irradiation sickness, and the reduced incidence of the major complications of polycy- [illegible]

leagues and I believe is offset by the marked reduction in the incidence of thrombosis and hemorrhage, the occasional development of severe hypoplasia of the marrow, and the fact that the long range effects of treatment with radioactive phosphorus are unknown However, as Lawrence has shown, the survival time of polycythemic patients treated with radioactive phosphorus is comparable to that of patients under treatment for diabetes mellitus or pernicious anemia

Nitrogen Mustard Methyl *bis* (*β* chlor ethyl) amine hydrochloride (HN_2) has been used in the treatment of polycythemia vera Remissions may be induced with total dosages of from 0 4 to 0 6 mg per kilogram of body weight, but they are usually of much shorter duration than the remissions induced by radioactive phosphorus Relapses are common in from 3 to 6 months after the initial course of treatment, and rarely do the remissions last more than a year This form of treatment does not appear to have any

particular advantage over the administration of radioactive phosphorus, and it has the disadvantages of the need for hospitalization during treatment, the frequent occurrence of nausea and vomiting following administration of the drug the induction of remissions of short duration, and the fact that the long range effects of this form of treatment are unknown

Diet. A diet low in iron has been recommended as an adjunct to other forms of therapy on the basis of the hypothesis that a reduced intake of iron would result in diminished production of erythrocytes (Dameshek and Henstell) While the synthesis of hemoglobin may be inhibited by such a diet, there is no conclusive evidence that a low intake of iron materially reduces the rate of regeneration of erythrocytes A more logical approach would seem to be the inhibition of erythropoiesis by means of irradiation (spray irradiation or radioactive phosphorus) It has been our practice to administer iron to patients treated with radioactive phosphorus who have a deficiency of iron

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HEMOPHILIA

Hemophilia is a hereditary, sex linked recessive, constitutional anomaly of blood coagulation occurring in affected males and marked by prolonged hemorrhage and delayed coagulation time Although, theoretically possible in the female, no case has been reported

In view of its hereditary nature, no cure is to be anticipated although theoretically the incidence of the disease could be reduced by the restriction of propagation in those capable of transmitting the disease Actually, however, nonaffected males are the only *ones who are 100 per cent safe in this regard*

As soon as the diagnosis is established, the parents should be clearly informed as to the nature of the disease, the risks of surgical procedures and trauma No surgical procedure is too simple to be fatal and most patients will be chronic invalids by the time they are 20 years old The patient when old enough should likewise be instructed concerning risks

Intramuscular injections of all types and *sternal aspirations are to be avoided*, as disagreeable hematomas readily form

Hemarthrosis is best treated by rest and compression bandages during the acute phase and mild physical therapy as the hematoma begins to resorb Aspiration of the joint is hazardous and frequently fails

to shorten the convalescence Operations on joints should be undertaken only in unusual circumstances as a calculated risk with a high chance of failure and possible exsanguination

Small wounds are best treated locally with thrombin which precipitates fibrin instantly Such wounds must be clean, as the topical agent must be brought into direct contact with the bleeding surface A sustained pressure dressing may be used concomitantly Cautery may temporarily stop the bleeding, but a subsequent slough is likely to form and bleeding will again ensue, this time from a larger area Extractions of teeth are hazardous and may be fatal

The care of these patients is directed toward the preliminary reduction of the patient's coagulation time to as near normal as possible with transfusions of blood or antihemolytic globulin, local measures to control bleeding, and repeated small transfusions of blood as necessary during the period which bleeding may occur Thrombin or dried plasma may be applied locally, a partial denture may be used as a pressure dressing, or a bloodless extraction may be attempted by the rubber band method

Blood transfusions, which need not be large to be effective, continue to be most successful in lowering the coagulation time to normal Fresh whole blood or plasma are the most dependable, but stored blood and stored, frozen, or lyophilized plasma are also effective The quantity transfused will depend on how much blood has been lost and must be replaced as well as on how much blood is necessary to restore the coagulation time to normal If whole blood is not available or is unnecessary, 100 to 250 cc of plasma may be administered for its antihemophiliac qualities alone This effect persists for 6 to 12 hours and is maximal in one hour

In more recent years, particularly during the [illegible]

[illegible] have been almost as effective as fresh whole blood in shortening the coagulation time However, a refractory state may develop with its repeated use This is less apt to occur from the use of blood or blood plasma

Injections of fresh and lyophilized plasma twice weekly have been used prophylactically with prolongation of the interval between hemorrhage

The mortality rate from major operations in cases of hemophilia is inordinately high, and operation should be avoided whenever an alternative exists The acute abdomen has long constituted one of surgery's imperative emergencies Recently, however, antibiotics in adequate amounts have greatly lessened the risk of peritonitis, thus permitting safe observation over a somewhat longer period of time, ultimately, perhaps, even obviating the need for surgery altogether

It is also clear that in many cases of peritonitis, acute appendicitis and occasionally even intestinal obstruction are simulated by or due to retroperitoneal or submucosal hemorrhage Thus, the decision to operate is beset by many difficulties and the need for temporizing is emphasized

If, however, operation is considered to be unavoidable, the coagulation time should be brought as nearly to normal as possible, blood should be given freely in small amounts at frequent intervals, and a local hemostatic agent, such as thrombin, used with the customary careful surgical methods

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PURPURA

Idiopathic Thrombocytopenic Purpura The value of any therapeutic measure must inevitably be considered in relation to the natural history of the disease This is true in idiopathic thrombocytopenic purpura,[1] a cyclic disease, tending to spontaneous remissions A gradient from young to old may be noted The young are most frequently affected, most frequently undergo spontaneous remissions, and are most benefited by accepted therapy The disease becomes increasingly uncommon among persons more than 30 years of age and rare among those more than 50 years of age In addition, it must be noted that adult males are seldom affected

It may seem superfluous to reiterate the

repeated injunction, "be certain of the diagnosis," yet even the experienced observer may be deceived by clinical appearances and saved only by confirmation of the diagnosis by observations of the bone marrow With the technic of sternal aspiration so highly developed, probably no patient should be subjected to splenectomy without this having first been done

Approximately 35 to 40 per cent of patients may be expected to undergo permanent spontaneous remissions This is particularly true of infants Obviously any form of treatment will be effective in this group

The rest may temporarily improve, fail to improve, or progress rapidly to a fatal issue

though platelets agglutinate shortly after withdrawal of blood blood from the blood bank may be used successfully Apparently the agglutinated platelets are still functionally active However, fresh blood is to be preferred The amount of blood given will depend on the physician's preference as well as the patient's condition Generally speaking, transfusions of 500 cc of blood are tolerated well if the rate of delivery is not too fast

Transfusions may be used preoperatively to prepare a patient who is severely ill for splenectomy or to protect a patient during his first episode when operation is refused or for other reasons a conservative course is pursued

Allen and his associates described the occurrence of a heparin like substance in idiopathic thrombocytopenic purpura which responded to an inhibitory effect of antiheparin toluidine blue or protamine administered intravenously Either was administered in daily doses of 1 to 4 mg per kilogram of body weight in 250 to 500 cc of normal saline solution over a 2 hour period More recently larger doses have been used An initial dose of 2 5 mg per kilogram of body weight was usually satisfactory A dose of 1 5 to 2 mg per kilogram was given thereafter until bleeding stopped (usually in 24 to 48 hours) after which time it was administered every 2, 3, or 4 days, or as bleeding recurred

Our own experience with this method has been discouraging and we have not been able to duplicate the proponents' good results

Other methods of treatment, including the use of snake venom testosterone, vitamins and so forth are of doubtful value A diet high in protein and supplementary iron should be employed if loss of blood of any significant degree occurs

Splenectomy, as it becomes safer with improved methods, assumes a more prominent place in the therapy of this disease Elliott reported no operative deaths in a series of 62 splenectomies for this disease Curtis had one death in 22 consecutive splenectomies for thrombocytopenic purpura The long time operative mortality—in the cases observed at the Mayo Clinic has been approximately 5 per cent The eventual mortality in cases in which splenectomy is not carried out is probably in excess of 12 per cent Except for the risk of splenectomy which is approaching a negligible figure the

tient temporized with too long It is held that the finding of eosinophilia of the bone marrow indicates a more favorable prognosis with a tendency to spontaneous recovery This is not infallible, however, as we have observed a fatal outcome from cerebral hemorrhage in such a case in which splenectomy was too long deferred

Elliott noted successful results among 95 per cent of patients less than 31 years of age on whom splenectomy was done Among those 31 or more years of age only 43 per cent obtained good results, making an over all figure of 77 4 per cent good results, twice the 36 per cent good results for patients treated medically This compares well with the figures presented by Curtis, Wintrobe, and investigators at the Mayo Clinic

After splenectomy thrombocytopenia may persist with or without bleeding or after an initial rise in platelets, thrombocytopenia may recur When it occurs, it presents an exceedingly distressing problem Accessory splenic tissue has been implicated frequently and in at least one instance apparently removed with benefit Attempts at the clinic have not been so gratifying In one instance,

five accessory spleens of fair size were delineated preoperatively with thorotrast and all subsequently removed at operation without, in the least, affecting the unfavorable course In another case exploratory operation was performed without accessory splenic tissue being found Following a turbulent postoperative course, a satisfactory remission occurred which has persisted for more than a year All decisions in such cases are perilous and uncertain

Secondary Thrombocytopenic Purpura Secondary or symptomatic thrombocytopenic purpura occurs in conjunction with some other primary disease or disturbance Among these are the blood dyscrasias (the leukemias lymphomas, multiple myelomas, aplastic and pernicious anemia), metastatic malignant lesions, Gaucher's disease, acute infections, hepatic disease, hypersplenism, and drug intoxication The following drugs and chemical agents are known to precipitate thrombocytopenic purpura organic arsenicals, gold salts, benzene, allyl-isopropyl acetyl-carbamide (sedormid) dinitrophenol, quinine, ergot, sulfonamides, thiourea and sodium salicylate

Treatment is directed toward the correction or amelioration of the underlying process Contact with possible offending drugs or chemical agents should be removed Blood transfusions may be of temporary benefit in the control of bleeding if it becomes a problem Splenectomy is of value in Gaucher s disease associated with a secondary thrombocytopenic purpura, in hypersplenism, and occasionally in cases of lymphoma with thrombocytopenia

BAL in adequate amounts is of proved value in the treatment of thrombocytopenic purpura resulting from heavy metal poisoning such as occasionally occurs in chrysotherapy or antisyphilitic treatment with organic arsenicals Splenectomy has been performed successfully in such cases

Sedormid causes thrombocytopenic purpura in individuals sensitive to it, although, in the early stage, the bone marrow may show no depletion of megakaryocytes

Thrombotic Thrombocytopenia Since 1925, 14 cases of acute purpura with associated platelet thrombi, thrombocytopenia and fever, anemia, and a rapidly progressive fatal course have been reported (Fitzgerald et al) Of the patients affected, 11 have been females, 3 males, 11 were 34 years of age or younger Splenectomy was done in 2 instances without success The cause is not known and no effective form of treatment has been found

Nonthrombocytopenic or Vascular Purpura Capillary purpura due to allergy (Schonlein Henoch purpura), an inadequately understood syndrome, results from increased permeability of the capillary bed Hematopoiesis is undisturbed Symptoms occur whenever exudation takes place The skin, gastro intestinal tract, and joints are most frequently involved If an underlying cause can be discovered, it should be removed Adrenalin 0 5 to 0 1 cc of 1 1000 solution given subcutaneously may be of help in relieving the skin manifestations, calcium salts intravenously may relieve intestinal symptoms

Recurrences are common, but the prognosis is generally good, although extensive hemorrhage into a vital center can occur Since vascular purpura is essentially an affliction of children and young adults, improvement may occur spontaneously with advancing age

Purpura simplex is a benign hereditary familial disturbance affecting all parts of the body, but principally the extremities It may come on at any age, occurs chiefly in women, and needs no treatment

Symptomatic vascular purpura may be due to trauma, senility, orthostasis, infection, liver disease, avitaminosis, snake venom, and drugs Treatment consists of recognition and removal of the underlying process

Edwin D Bayrd

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MULTIPLE MYELOMA

Myeloma a plasmacytic neoplasm involving the bone marrow and to a lesser degree the viscera, may be observed in a localized generalized or leukemic form Its treatment has always been an exceptionally distressing problem for doctor and patient alike as it is not only a uniformly fatal disease but often an agonizingly painful one Palliation of the symptoms management of the complications and specific treatment will be considered

Pain is the most prevalent most distressing and most difficult symptom to control A number of general measures have been employed with varying success against it Their relative values in any group of cases are unimportant since they cannot be used as a basis for predicting individual responses

Roentgen therapy the oldest method of treatment is the most widely used It is the treatment of choice in local lesions, best used in conjunction with surgical excision if the lesion is accessible For the diffuse disease it is often helpful in relieving distress and occasionally will be accompanied by regression of bone lesions In cases in which its effectiveness has been demonstrated it may be repeated several times with benefit The development of leukopenia however, may prevent its use

Radiophosphorus has about the same range of usefulness as roentgen rays in the generalized form of the disease We have seen one patient in a terminal stage of the leukemic phase undergo a remission following the administration of a little over 6 0 millicuries of this drug It has been our practice to administer 1 5 to 2 5 millicuries of radiophosphorus intravenously each week until improvement occurs or neutropenia begins to develop It has no unpleasant side effects, is easy to give but possible suppression of the bone marrow is a risk to be appreciated

4 4' Diamidinostilbene (stilbamidine), 4, 4' - (pentamethylenedioxy) dibenzamidine (pentamidine), and antimony, parenterally administered, have also produced relief of pain in some patients Stilbamidine has been most widely used (Snapper) As advocated, this drug is dissolved in 10 cc of sterile distilled water and injected intravenously 30 minutes after the patient has received a hypodermic injection of 1/150 gram (0 00043 gm) of atropine Fifty milligrams are given the first day, 100 mg the second and 150 mg daily thereafter in conjunction with a diet low in animal protein Good results in some cases have also been obtained without dietary restrictions A course consists of 20 injections, but may be repeated Its use is contraindicated in the presence of renal failure

Immediate unpleasant side effects, minimized by atropine, may include burning paresthesia formication, nausea, vomiting unconsciousness, and convulsions A late side effect (2 5 to 5 months later) is trigeminal neuropathy with burning itching and dissociated anesthesia This usually subsides spontaneously but may persist for months

Injections of procaine or dolamin may be helpful in blocking pain of a restricted distribution Orthopedic measures, such as the use of a Taylor brace or belt and reduction of pathologic fractures, are often necessary Laminectomy may relieve transverse myelitis Daily water diuresis may protect a patient with Bence Jones proteinuria from nephron nephrosis," and blood transfusions are useful in relieving the anemia Once uremia develops, the outlook is critical

Until recently there was no specific treatment for this disease However, confirmation of Alwall s observation of a complete clinical and hematologic remission following the prolonged use of urethane in one of 2 cases of multiple myeloma has stimulated renewed interest in this drug which is at present the agent of choice About 50 per cent good results are claimed There can be no doubt that in some cases complete remission has resulted

Fairly large doses of urethane (3 to 6 gm. daily) of either the elixir or coated tablet are advocated This must be continued for 4 to 8 weeks at which time the dose may be reduced or discontinued, depending on

the patient s response and the development of leukopenia The primary objective should be a sustained high level of the drug over a long period of time Although good results have been reported with smaller doses and [illegible]

this for at least 3 months Even so we have found large doses of urethane to be poorly tolerated and have been generally disappointed with the results in most of our patients One has received more than 1000 gm without appreciable effect on his disease Nevertheless despite the uncertainties no other form of therapy offers the possible benefits of urethane at present

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CHAPTER X

DISEASES OF THE URINARY TRACT

The treatment of renal diseases is still in a state of uncertainty because the pathologic physiology of renal diseases has not been fully worked out The treatment therefore, must be largely symptomatic In the past, it was well recognized that a damaged kidney was to be given rest by certain dietary re

day with a better knowledge of kidney function the fundamental basis of treatment still is the reduction of the work of the kidney, by dietary measures

What will be said in the following pages regarding the treatment of kidney diseases, while not absolute will give the reader an indication of the clinical methods used to combat the disorders When a patient is in need of aid a physician is called on to use his clinical experience as a guide to therapy despite the controversy on the theory of the disease itself

ACUTE GLOMERULONEPHRITIS

Volhard pointed out long ago that time is the most important factor in the treatment of acute glomerulonephritis While acute nephritis may commence abruptly with the *clinical features of hypertension or acute* renal or cardiac insufficiency, there are also cases of slow development in which the patient complains of headache, anorexia, and fatigue, and at times of nothing at all It is necessary, therefore, to be on the alert for acute nephritis after acute tonsillitis and other infections just as formerly we were *after scarlet fever*

The treatment of acute glomerulonephritis may be divided into two categories (1) the treatment of the abrupt, stormy type of the disease, and (2) the treatment of the *milder* forms Only a comparatively small number of patients ever suffers from the form which begins abruptly and runs a stormy course The milder kind is more common, and the chief dangers of genuine uremia, convulsions and heart failure are rare in these milder types

Treatment of the Abrupt, Stormy Type The principal therapeutic measures in the abrupt phase of nephritis are control of high blood pressure, convulsions, heart failure *and promotion of a diuresis to ward off* uremia

Hypertension per se seldom does direct damage but indirectly it may be the motivating factor causing pronounced edema of the brain with convulsions or sudden heart failure Blackfan showed, in 1923, that blood pressure may be lowered and convulsions controlled by the intravenous use of 1 per cent magnesium sulfate Today this is accomplished by giving 15 to 30 grains (2 to 3 gm) of magnesium sulfate two or three times a day depending on the clinical condition and requirements of the case Rubin and Rapoport have reported favorable re*sults with the administration* of 45 grains (3 gm) of magnesium sulfate dissolved in 120 cc of 5 per cent glucose solution twice a day or oftener, depending on the blood pressure and the general condition *of the* patient If possible, it is well to determine precisely the level of the magnesium in the *blood Occasionally, following* the use of magnesium sulfate, respiratory embarrassment may occur, and it is necessary, therefore to have calcium gluconate ready for intravenous injection to combat the magnesium sulfate action This may be given in doses of 30 grains (2 gm) in 50 cc of 5 per cent glucose, or two 10 cc ampules

... to be giving

several times a day Chloral hydrate and sodium bromide, 30 grains (2 gm), may also be dissolved in 200 cc of water and given by rectum by the Murphy drip method

Myocardial failure is a common complication in acute nephritis especially when high blood pressure is present and digitalis 1½ grains (0 1 gm) intravenously three times a day or strophanthin 1/400 grain (0 0006 gm) intravenously intramuscularly or subcutaneously repeated every 2 hours for four or five doses may be given Purified glycosides of digitalis such as digitoxin or digoxin both in doses of 0 25 mg or any of the other standard preparations may be used instead of digitalis Caffeine sodium benzoate 3 grains (0 2 gm) every 3 hours intramuscularly or subcutaneously has been used but I feel that it is not nearly so satisfactory as digitalis or strophanthin When heart failure sets in especially if hypertension attends it a venesection of 500 cc of blood may be of value

As there is always an increase of the blood volume in acute nephritis the administration of intravenous fluids must be given with great caution for the addition of fluid to the already overloaded vascular system may provoke an attack of heart failure Once heart failure sets in in such cases it is difficult to reverse or correct It is far better to take the proper measures to prevent the onset of an attack

If the kidneys cannot be made to function again or if oliguria or anuria does develop uremia may be imminent unless diuresis can be established Of most importance as a diuretic agent is water but other simple diuretics may be used such as potassium citrate 20 grains (1 3 gm) three or four times a day or a combination of potassium acetate and potassium citrate each 20 grains (1 3 gm) three or four times a day or a combination of potassium acetate and potassium citrate each 20 grains (1 3 gm) three times a day in liquor ammonii acetatis Stronger diuretics are contraindicated in the treatment of acute nephritis

Frequently when a patient is unable to take adequate fluids by mouth consideration must be given to the use of intravenous fluids The kind and amount to be given may be summarized briefly as follows (1) Whole blood plasma or albumin when severe anemia or reduction in plasma protein occurs this however is seldom used as the anemia in acute glomerulonephritis is not so severe (2) Physiologic saline when there is hypochloremia or alkalosis due to vomiting and dehydration Alkalosis is rare in acute nephritis as acidosis usually develops usually 1000 cc every 12 hours for a few doses is sufficient to correct this abnormality (3) Glucose solutions 5 10 and 50 per cent the weaker ones when there is dehydration and it is necessary to replenish body fluids and the strongest solution when dehydration and diuresis are desirable (4) Alkaline solutions such as sodium bicarbonate 7 5 per cent intravenously and 1/6 molar sodium lactate 1000 cc daily or more as necessary in the presence of acidosis as determined by a CO_2 combining power of below 40 vol per cent (5) Calcium chloride solutions or ammonium chloride solutions to combat alkalosis It must be emphasized again that when heart failure is imminent one must inject intravenous solutions slowly if at all as the danger of intravenous fluid to the heart depends more on the speed of administration than on the volume or kind of fluid administered

Attempts have been made to revive a method advocated by Volhard and called the "water thrust" in which 1200 to 1500 cc of water or weak tea are given within a period of a half hour if starvation and other methods of treatment fail to promote diuresis This method however has not been popular with most observers

There is no rigid rule regarding the restriction or administration of fluids but my observations have led me to restrict fluids if a patient has hypertension with increased intracranial pressure and to administer as much as 2000 cc a day if these clinical findings are not present If the nonprotein nitrogen has risen and an oliguria is becoming more accentuated fluids may be given in optimal amounts When there is a kidney shut down it is not logical to force fluids intravenously as damage may result when attempting to do so When hypertension

cases is to improve the urinary output which in turn augments the output of nitrogenous substances When there is no satisfactory response to the administration of intravenous fluids they should not be forced

Edema is not the criteria on which to base the administration or restriction of fluids as in cases without hypertension but with oliguria and rising nonprotein nitrogen fluids are given in spite of edema

Treatment of the Milder Form In the milder forms of the disease complete bed rest *until the* kidney lesion is healed and a regulated diet with special attention to the protein salt and fluid intake are most important to consider

The main factor in the treatment of the kidney lesion of nephritis is of course rest and other methods of treatment employed aim to bring about the fulfillment of this requirement The importance of rest is difficult to visualize in the management of nephritis because there is no pain and no apparent unfavorable consequence of exercise Rest for the inflamed kidney is accomplished by reducing the amount of exercise and work the patient is required to do thereby cutting down the metabolic requirements of the body which relieves the work load of the kidney Murphy and Peters emphasized the importance of rest in an investigation of 89 patients with acute nephritis Forty one were completely cured when they remained in the hospital until well while 48 who left the hospital before cure was accomplished fared less well eventually

Enforced bed rest admittedly may be difficult especially in younger patients but if a complete recovery is to be accomplished this form of therapy cannot be emphasized too strongly After one month if hypertension edema and azotemia have subsided and the urine cleared quite well a patient may be allowed bathroom and armchair privileges if after 4 or 5 months a patient is cured except for urinary changes further enforced rest seems futile for the patient may be considered to have an unhealed case

a diet having a low protein content From the experimental work of Addis Farr and Smadel and Chanutin and Ferris it is agreed that an injured kidney heals much faster when a low protein diet is given As I have pointed out elsewhere a moderately high protein diet not only fails to correct the hypoproteinemia but it actually causes

make "bigger and better kidneys" but the patient dies in uremia

Generally speaking a diet containing 0 50 to 1 0 gm of protein per kilogram of body weight represents the optimal diet for the nephritic since it fulfills protein requirements adequately and still *does not retard* healing of the kidney Vitamin supplements in these diets especially A and D are recommended not only because of added nutritional value but also because they elevate the resistance of the patient s upper respiratory tract to infections which so often lead to renal inflammatory lesions Vitamins A and D may be given in the form of cod or halibut liver oil capsules B complex in brewers yeast supplemented by intramuscular injections of thiamine chloride 2 to 3 cc. daily Vitamin C may be given in tablet form. Iron in the form of iron ammonium citrate 10 grains (0 66 gm) three times daily may

it is felt that patients progressed as satisfactorily on one diet as on the other as these diets did not seem to retard or augment the healing of the renal lesion

Salt and fluid intake is another problem in the treatment of the acute nephritic and while the exact nature of the effect of salt on the kidney is still questioned it is generally believed that salt does add work for the kidney The amount of fluid that should be given a patient as has been pointed out above varies with the degree of renal insufficiency However it is felt that the administration of large quantities of fluid has no adverse effect on the kidney It is my practice to reduce the sodium chloride to 1 0 to 2 0 gm a day This may be reduced to 1 0 gm daily if edema persists

Most authorities advocate the removal of infection such as diseased tonsils foci of infection in sinuses or apical abscesses about one month after the acute episode While statistics may fail to provide evidence of the benefit of such removal the individual patient often shows striking benefit

The surgical treatment of nephritis ie decapsulation of a kidney in the treatment

of anuria, has proved beneficial in certain select cases of acute anuria Decapsulation is based on the theory that the resulting decapsulation of the kidney allows a greater blood flow Most reports have not shown gratifying results from this method of treatment I believe this procedure is indicated when there is an anuria lasting for 7 days or more which has resisted the simpler therapeutic measures

FRANCIS D MURPHY

SUBACUTE GLOMERULONEPHRITIS

Subacute glomerulonephritis may be called a second or later stage of unhealed acute glomerulonephritis with a progressive downward course and ending fatally after a short stormy period Treatment, to a large extent, is the same in subacute nephritis as in the acute form

The primary aim is to promote a diuresis This is accomplished by giving an adequate amount of fluid, preferably a milder alkaline one Sometimes theobromine or some other xanthine 10 grains (0 6 gm), may be given two or three times daily Salyrgan novasurol and any of the mercurial diuretics are contraindicated Magnesium sulfate or any of the saline cathartics may prove beneficial though at times there is such an outpouring of fluid into the pleural pericardial, or peritoneal sac that repeated tapping is necessary to remove it from the cavities

As in the treatment of the acute phase, a high caloric diet with a moderate amount of protein is indicated as well as iron tonics such as iron and ammonium citrate, 15 grains (1 gm), three times daily or tincture of nux vomica 10 minims (0 6 cc), three times daily Fluid and salt limitations to about 1200 cc a day seem effective in controlling the edema in this form of nephritis

FRANCIS D MURPHY

THE NEPHROTIC SYNDROME

The term "nephrotic syndrome" is used to designate a clinical condition which occurs in its purest form in genuine lipoid nephrosis and in certain types of chronic glomerulonephritis in which the tubular system is predominantly involved A combination of factors which produces the characteristic clinical picture of the nephrotic syndrome

sence are hypertension, hematuria, azotemia, and uremia

Depending on the nature of the basic renal disease the main features of the nephrotic syndrome vary in degree as, for example, in genuine lipoid nephrosis the heavy albuminuria, excessive edema marked lowering of the plasma albumin, and a decided hyper

drome the degree of edema albuminuria, and other features may vary considerably

In the treatment of the nephrotic syndrome it makes a difference if the glomeruli of the kidney are extensively disordered or if the tubules are badly damaged with the glomeruli slightly involved This is particularly true when a high protein diet is considered for the treatment of the hypoalbuminemia When the glomeruli are badly damaged it is a dangerous thing to give a high protein diet because this leads to further glomerular break down Hypertension hematuria and azotemia are the chief manifestations of glomerular activity However, with the glomeruli practically intact, a high protein diet does no damage to the disordered tubules

It is the control of the edema which occupies the chief attention in the treatment of the nephrotic syndrome This however de

dependent on the adequate control of sodium in the diet and the proper use of fluids The hypercholesterolemia and the doubly refracting lipoids in the urine require no special treatment as they tend to disappear when the other factors are controlled

One of the characteristic manifestations of the nephrotic syndrome is the continuous loss of large amounts of protein in the urine, and a high protein diet is believed to lead to some diuresis by reason of the increased urea that is formed (Christian) Protein intake, therefore, should be as high as is indicated for the individual patient For the

patient with chronic nephritis, 0 75 gm to 1 0 gm per kilogram of body weight seems to be the optimal amount of protein intake If the nephrotic syndrome occurs with a minimal amount of glomerular damage, the protein intake may be augmented to 1 5 to 2 0 gm per kilogram of body weight or higher if the patient tolerates it Epstein was one of the first to advocate a high protein diet to replenish the plasma protein which had become reduced from albuminuria, and at the present time a diet of approximately 1 0 gm of protein per kilogram of body weight per day is considered an optimal amount to be given a patient If the non protein nitrogen of the blood rises, a reason able restriction may become necessary If the nitrogen equilibrium is not maintained, however, malnutrition, anemia, and cachexia are clinical features that may develop Blood transfusions until the blood is normal or nearly normal have been tried, and it has been proved that they are of little benefit and may be dangerous if acidosis is severe (Salvesen) Farrar et al have recommended an acid-ash high protein low sodium diet which is excellent for patients with the ne phrotic syndrome Initially, they point out that six small feedings daily will supply a patient with about 60 gm of protein Each feeding is composed of one cup of milk and one egg or two slices of bread or one cup of cereal with butter, sugar spices and flavor ing as desired The next stage of the diet (90 to 130 gm of protein daily) consists of three to six meals providing at least two or three eggs, ¼ or ½ pound of meat, fish, or fowl, and six slices of bread or servings of cereal Not more than two cups of milk, one cup of vegetables, and one cup of fruit is indicated, while sugar, butter, gelatin, prunes, plums and cranberries may be eaten as desired The foods and foodstuffs to be avoided are the following salt, soda, salted butter, salt bread or salted meat cheese (except cottage), lima beans, spinach, dates and raisins A special liquid diet designed to supply a liberal protein, high calorie, and low sodium diet has been described by Spence and Sutton, for it has been their ex perience that normal diets may prove difficult to administer by the usual methods, particu-larly during the edematous phase of the disease

Human albumin, in preference to human pooled plasma which contains a consider able amount of salt, has been determined as a nearly ideal diuretic agent for patients having the nephrotic syndrome associated with a low colloid osmotic pressure due to reduced serum albumin At the present time however, the only limiting factor is its ex pense The optimal amount of human albu min for a patient per day is 30 to 60 gm given intravenously

Amino acid therapy has been used in mal nutrition as a source of improving serum albumin levels and to induce a positive nitro-gen balance However, there is some evi dence to show that serum albumin is a more effective way of satisfying the nitrogen def icit Amino acids can be prepared in pure crystalline form, although the expense in curred limits their use to special studies Preparations containing amino acids are now being manufactured in pure enough form to be given parenterally, however, to maintain plasma protein and nitrogen levels Protein hydrolysate, 50 to 100 gm may be given orally or intravenously daily For intrave nous injection 5 per cent solution in 5 per cent dextrose in distilled water at a rate of 5 to 20 gm of amino acids per hour is given (Farrar et al) Thus far amino acid therapy has some distinct disadvantages Orally it is unpalatable, and for any administration has a relatively high sodium content There has been no conclusive evidence to show that oral administration of protein hydrolysates is more effective than oral administration of formed proteins

Acacia, in doses of 500 cc of 6 per cent acacia and 0 06 per cent sodium chloride in distilled water given intravenously, alter nating with intravenous doses of 2 cc of mercuhydrin every other day, has also been used to bring up the colloidal pressure If injected slowly, it disappears slowly from the blood has a replacement value for the hypoproteinemia and causes only slight or no reactions Unfavorable aspects such as deposition and irritation of the liver and to a less extent the spleen and kidney, however have been known to occur and have caused its use to be limited Smalley et al, after experimentally administering large amounts of acacia to dogs and subsequently observing the liver, spleen, and kidneys, found the

liver enlarged, vacuolation of the cells, and varying amounts of acacia present in the organs but no evidence of important damage They conclude that acacia is not contra indicated in the therapy of the nephrotic syndrome Gelatin and globin 25 to 50 gm per day have been used in the same way as acacia, are inexpensive, and seem to be of some value

While formerly water and salt restriction were of primary concern in managing pa tients with edema, at present it is only salt which is eliminated from the diets while

the patient has no edema however there is no real need for restricting salt so completely and probably 2 to 3 gm a day would be an optimal amount

One of the things to remember in the treatment of the nephrotic syndrome is that its presence does not necessarily require the restriction of fluid Restriction may cut down the excretion of nitrogen and augment chances of uremia while the administration of fairly large quantities of water may act as a diuretic influence and improve the output of nitrogenous substances There is more than one opinion concerning the optimal amount of fluid to be given to these patients Some believe that the fluid should be restricted others that there should be a normal or op timal amount of 1500 to 3000 cc per day, and finally, there are those who think that over 4000 cc a day may be given with bene fit The best course to follow is to give an optimal amount (2500 cc) of fluid a day, and if diuresis does not occur satisfactorily the fluid may be increased Christian believes that about 1000 to 1200 cc of fluid should be given daily unless this leaves the patient un comfortably thirsty If so fluids need to be increased He also advocates the use of parenteral fluids in the form of 5 to 10 per cent aqueous glucose solution but not glu cose in normal saline when fluid loss is caused by diarrhea or vomiting Basically, the out put of urine is the kidney s primary function and an adequate fluid intake is one of our best assurances that an adequate output of urine and the toxic substances of metabolism will be preserved

Diuretic *drugs such as the mercurials,* thiomerin urea, and the acid forming salts, often may cause a marked diuresis weight fall and decreased edema, but these drugs are to be used reluctantly as they may be more detrimental than beneficial Many au thors have challenged the use of diuretics because of the damage they may inflict on the renal tubules, but it is felt that in cardiac edema where the kidney is swollen and con gested the mercurials often may aid in clear ing up an already present albuminuria In renal edema however, diuretics should be used reluctantly and only when all other measures have failed

Of the mercurial diuretics, mercupurin mercuhydrin and mercurophylline are the most satisfactory and may be given intra venously 2 cc every 3 or 4 days orally in suppository form for rectal use only or intramuscularly (thiomerin is given subcu taneously) Serious toxic manifestations such as stomatitis colitis hematuria or circula tory collapse are rare unless circulatory fail ure or nitrogen retention exists Digitalis may prove beneficial and even a lifesaving meas ure at this time for patients with cardiac edema although digitalis used in patients with renal edema is of no value as a diuretic agent

determinations of the blood urea nitrogen should also be done during its use This preparation is contraindicated when azote mia is present

The acid producing salt ammonium chlo

pointed out that after absorption the am monia (NH_4) radical becomes involved in

the excessive chloride ion by the kidney requires the excretion of sodium When the sodium is lost a certain ratio of water is also carried off It must be remembered that the kidney has a defense mechanism which limits the effect of ammonium chloride If one gives 10 gm of ammonium chloride a day, on the first day sodium is lost The

patient with chronic nephritis, 0 75 gm to 1 0 gm per kilogram of body weight seems to be the optimal amount of protein intake If the nephrotic syndrome occurs with a minimal amount of glomerular damage, the protein intake may be augmented to 1 5 to 2 0 gm per kilogram of body weight or higher if the patient tolerates it Epstein was one of the first to advocate a high protein diet to replenish the plasma protein which had become reduced from albuminuria, and at the present time a diet of approximately 1 0 gm of protein per kilogram of body weight per day is considered an optimal amount to be given a patient If the non protein nitrogen of the blood rises a reason able restriction may become necessary If the nitrogen equilibrium is not maintained, however, malnutrition, anemia, and cachexia are clinical features that may develop Blood transfusions until the blood is normal or nearly normal have been tried, and it has been proved that they are of little benefit and may be dangerous if acidosis is severe (Salvesen) Farrar et al have recommended an acid-ash high protein low sodium diet which is excellent for patients with the nephrotic syndrome Initially, they point out that six small feedings daily will supply a patient with about 60 gm of protein Each feeding is composed of one cup of milk and one egg or two slices of bread or one cup of cereal with butter, sugar spices, and flavoring as desired The next stage of the diet (90 to 130 gm of protein daily) consists of three to six meals providing at least two or three eggs, ¼ or ½ pound of meat, fish, or fowl, and six slices of bread or servings of cereal Not more than two cups of milk, one cup of vegetables, and one cup of fruit is indicated, while sugar, butter, gelatin, prunes, plums, and cranberries may be eaten as desired The foods and foodstuffs to be avoided are the following salt, soda, salted butter, salt bread, or salted meat, cheese (except cottage), lima beans, spinach, dates, and raisins A special liquid diet designed to supply a liberal protein, high calorie, and low sodium diet has been described by Spence and Sutton for it has been their experience that normal diets may prove difficult to administer by the usual methods, particularly during the edematous phase of the disease

Human albumin, in preference to human pooled plasma which contains a considerable amount of salt, has been determined as a nearly ideal diuretic agent for patients having the nephrotic syndrome associated with a low colloid osmotic pressure due to reduced serum albumin At the present time however, the only limiting factor is its expense The optimal amount of human albumin for a patient per day is 30 to 60 gm. given intravenously

Amino acid therapy has been used in malnutrition as a source of improving serum albumin levels and to induce a positive nitrogen balance However, there is some evidence to show that serum albumin is a more effective way of satisfying the nitrogen deficit Amino acids can be prepared in pure crystalline form although the expense incurred limits their use to special studies Preparations containing amino acids are now being manufactured in pure enough form to be given parenterally, however, to maintain plasma protein and nitrogen levels. Protein hydrolysate, 50 to 100 gm, may be given orally or intravenously daily For intravenous injection 5 per cent solution in 5 per cent dextrose in distilled water at a rate of 5 to 20 gm of amino acids per hour is given (Farrar et al) Thus far amino acid therapy has some distinct disadvantages Orally it is unpalatable, and for any administration has a relatively high sodium content There has been no conclusive evidence to show that oral administration of protein hydrolysates is more effective than oral administration of formed proteins

Acacia, in doses of 500 cc of 6 per cent acacia and 0 06 per cent sodium chloride in distilled water given intravenously, alternating with intravenous doses of 2 cc. of mercuhydrin every other day, has also been used to bring up the colloidal pressure If injected slowly, it disappears slowly from the blood, has a replacement value for the hypoproteinemia, and causes only slight or no reactions Unfavorable aspects such as deposition and irritation of the liver and to a less extent the spleen and kidney, however have been known to occur and have caused its use to be limited. Smalley et al., after experimentally administering large amounts of acacia to dogs and subsequently observing the liver, spleen, and kidneys, found the

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The best course to follow is to give an timal amount (2500 cc) of fluid a day, d if diuresis does not occur satisfactorily e fluid may be increased Christian believes at about 1000 to 1200 cc of fluid should be ven daily unless this leaves the patient un mfortably thirsty If so fluids need to be creased He also advocates the use of renteral fluids in the form of 5 to 10 per nt aqueous glucose solution but not glu se in normal saline when fluid loss is caused diarrhea or vomiting Basically, the out t of urine is the kidney's primary function d an adequate fluid intake is one of our st assurances that an adequate output of ine and the toxic substances of metabolism ll be preserved

Diuretic drugs, such as the mercurials, thiomerin, urea and the acid forming salts, often may cause a marked diuresis weight fall, and decreased edema, but these drugs are to be used reluctantly as they may be more detrimental than beneficial Many au thors have challenged the use of diuretics because of the damage they may inflict on the renal tubules, but it is felt that in cardiac edema where the kidney is swollen and con gested the mercurials often may aid in clear ing up an already present albuminuria In renal edema, however, diuretics should be used reluctantly and only when all other measures have failed

Of the mercurial diuretics, mercupurin mercuhydrin and mercurophylline are the most satisfactory and may be given intra venously 2 cc every 3 or 4 days orally, in suppository form for rectal use only, or intramuscularly (thiomerin is given subcu- taneously) Serious toxic manifestations such as stomatitis, colitis hematuria, or circula tory collapse are rare unless circulatory fail

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One of the things to remember in the treatment of the nephrotic syndrome is that its presence does not necessarily require the restriction of fluid Restriction may cut down the excretion of nitrogen and augment chances of uremia while the administration of fairly large quantities of water may act as a diuretic influence and improve the output of nitrogenous substances There is more than one opinion concerning the optimal amount of fluid to be given to these patients Some believe that the fluid should be restricted, others that there should be a normal or optimal amount of 1500 to 3000 cc per day, and finally, there are those who think that over 4000 cc a day may be given with benefit The best course to follow is to give an optimal amount (2500 cc) of fluid a day, and if diuresis does not occur satisfactorily the fluid may be increased Christian believes that about 1000 to 1200 cc of fluid should be given daily unless this leaves the patient uncomfortably thirsty If so fluids need to be increased He also advocates the use of parenteral fluids in the form of 5 to 10 per cent aqueous glucose solution but not glucose in normal saline when fluid loss is caused by diarrhea or vomiting Basically, the output of urine is the kidney's primary function and an adequate fluid intake is one of our best assurances that an adequate output of urine and the toxic substances of metabolism will be preserved

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The acid producing salt, ammonium chloride is given in enteric coated tablets in an average dose of 10 to 30 gm per day In a recent therapeutic conference Marshall has pointed out that after absorption, the ammonia (NH_4) radical becomes involved in the general nitrogen metabolism of the body and disappears from the blood, leaving the chloride ion remaining Thus in effect the patient has received HCl The excretion of the excessive chloride ion by the kidney requires the excretion of sodium When the sodium is lost a certain ratio of water is also carried off It must be remembered that the kidney has a defense mechanism which limits the effect of ammonium chloride If one gives 10 gm of ammonium chloride a day, on the first day sodium is lost The

second day loss is not large the third day, sodium excretion will be normal We know that the mechanism of the kidney for producing ammonia is sluggish The production of ammonia the first day is slow but rises gradually to its peak on the fourth day As the ammonia continues to be produced the elimination of sodium is less Therefore in the use of ammonium chloride large doses are more effective than small doses and *large doses should be given* for the first 3 or 4 days and then stopped When the kidney is damaged it may be dangerous to give the acid producing salts because in advanced nephritis for example ability to form am

present Caution must be exercised therefore in using these acid producing salts in the presence of a damaged kidney Christian has mentioned that the ammonium salts seem to produce a minimum of gastro intestinal

little harm and disappears with a discontinuance of the drug

Potassium nitrate or potassium chloride has also been used in a similar fashion as ammonium chloride or ammonium nitrate However while patients receiving ammonium salts are guarded clinically against acidosis those receiving potassium salts should be watched for arrhythmias

Dried thyroid in 0 06 gm dosage daily and increased at weekly intervals is considered in the treatment of the nephrotic syndrome by many investigators as the basal metabolic rate is decreased in many patients having *this condition* However, it is my opinion that no benefits follow giving thyroid and in many instances thyroid intoxication nervousness or tachycardia may be the end result

In the treatment of the nephrotic syndrome the control of infection is an important consideration as in the past patients with this disorder died not of nephrosis nor of

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been a common cause of death in these cases *With the advent of the* antibiotics this complication has been found to be more easily controlled

In certain cases of nephrosis a condition known as "nephrotic crisis" may develop This is said to occur *when the plasma amino* acid nitrogen concentration drops below a

erysipelas which involves the edematous swollen tissues of the body Sometimes pneumonitis peritonitis or pleuritis may develop Usually the pneumococcus is the offending organism but the staphylococcus may also occur The exact cause and nature of nephrotic crisis is unknown

The intravenous injection of 5 per cent amino acid solution in 5 per cent glucose solution is indicated several times daily in the treatment of this disorder Some believe that regular administrations of solutions of amino acids are indicated in order to prevent the onset of these episodes For the fever and the infection penicillin in adequate doses of about 1 000 000 units a day provides gratifying results *

FRANCIS D MURPHY

CHRONIC GLOMERULONEPHRITIS

In the treatment of chronic *nephritis* there are two important factors which are closely related but for practical purposes may be considered separately (1) the kidney lesion itself (2) the numerous clinical *manifestations which are the result of* the alterations in the physiochemical balance of the body due to renal insufficiency Although the correlation between these two is poorly understood treatment is fairly satisfactory

the fact that cer

useful in these types of renal disease However it must be *emphasized that the observations presented* are of an experimental nature —*Editor*

Farnsworth E B Studies on the Influence of ... Nephr... in Simple

It is the control of the various imbalances of fluid electrolyte protein metabolism resulting from the kidney disease that is the chief object of treatment In addition it must be remembered that a patient having chronic nephritis may have a diminished kidney function due to gastro intestinal disturbances cardiovascular disorders cerebral conditions or general malnutrition These symptoms therefore should be considered more seriously in the general management of chronic nephritis and adequate quantities of food sufficient rest and recreation and the removal of any foci of infection which are indicated

Treatment of the Kidney Lesion Itself The treatment of the kidney lesion itself depends a good deal on the nature and the extent of the involvement of the structures of the kidney For example there may be extensive glomerular damage with minimal involvement of the tubules which leads to a clinical picture of hypertension hematuria and azotemia or there may be a minimal glomerular involvement with extensive tubular damage which produces a picture of extensive albuminuria edema and hypercholesterolemia and little or no hypertension hematuria or azotemia The combination present decides to a large extent the exact nature of treatment

In the treatment of the renal lesion itself there are three important factors to be considered rest diet and special drugs and therapeutic agents In these cases as in therapeutics in general rest is most important It is difficult to outline precisely the nature of rest necessary in chronic nephritis In certain other diseases such as angina pectoris and coronary insufficiency the pain is used as the guidepost for rest and relaxation but in kidney disease there is no pain and therefore it is hard to make an exact rule Rest to the kidney may be obtained in a direct way by keeping the patient at a minimal amount of physical activity and reducing his weight by proper dietary measures Obviously the amount of rest to be prescribed depends on how far the chronic nephritis has advanced

In the earlier stages a 50 per cent reduction in the patient s physical activity is probably all that is necessary later when renal function has become badly impaired the patient may be restricted to bed with only bathroom and armchair privileges The reduction of physical activity of course diminishes the metabolic requirements of the body and therefore reduces work for the kidney

Many observers believe that chronic nephritis may develop when patients with unhealed acute nephritis are fed a high protein diet on the other hand there are those who have proved that a high protein diet is not harmful to a patient with chronic nephritis It must be emphasized again that a patient with this form of renal disease may be in a debilitated condition and by restricting protein in the diet his nutrition may be further impoverished Therefore while it is difficult to lay down a rule of individual food requirements since food regulation varies with the various stages and forms of the disease nevertheless it is an accepted fact that management of the condition is centered around the protein salt and fluids of the diet In addition alcoholic beverages and tobacco should be restricted in most cases as they are usually harmful and the patient feels better when they are not used

The protein of the diet should be kept at a low level as it is generally accepted that an excessive amount of protein in the diet retards healing and makes the kidney disease worse What constitutes an optimal protein intake varies with different writers It is generally accepted now that 0 5 to 0 75 gm per kilogram of body weight is an acceptable figure

Sodium in the diet should not exceed more than 1 0 gm a day as there is an excessive amount of sodium chloride in the tissues Some of these therapeutic measures have been discussed previously under treatment of the nephrotic syndrome

As in protein regulation the fluid requirement in chronic glomerulonephritis varies greatly At the present time it is the consensus that about 1200 to 1800 cc of fluid is a moderate intake If the patient is sweat

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limited to from 800 to 1200 cc daily unless the kidney fails to excrete nitrogen or the renal function tests point to advanced functional impairment at which time

should be pushed In the presence of hyper tension fluids should be restricted if there is no renal insufficiency After a period of actual measuring of the fluid intake, the pa tient s thirst is a natural guide to the amount of fluid given

Many standard nephritic diets have been used Usually the

protein 8

Breakfast	Fruit—fresh stewed or dried cereal	½ cup
	Cereal	½ cup cooked or ⅓ cup dry cereal
	Milk	½ cup
	Bread or toast	2 slices with 1½ sq butter
	Cream	¼ cup
	Postum or kaffee hag	1 cup
Dinner	Meat—liver beef lamb mutton fowl fresh fish	1 slice ½" thick
	Potato rice or macaroni	½ cup
	Vegetable	½ cup
	Bread	1 slice with 1 sq butter
	Simple dessert—tapioca cornstarch pudding plain icecream custard etc	½ cup
	Milk	¾ cup
	Water	1 cup
2 30 P M	Water lemonade or orangeade	1 cup
Supper	Milk or	
	Cream soup (made without meat or meat stock)	1 cup
	Potato rice or macaroni prepared with milk cheese or egg	½ cup
	Vegetable	½ cup
	Salad preferably made with fresh vegetable	½ cup
	Bread	1 slice with 1 sq butter
	Fruit	½ cup
8 00 P M	Water orangeade lemonade	1 cup

Use no table salt and none in cooking unless prescribed by doctor
1 cup means 1 MEASURING cup
Occasionally substitute 1 cup of ovaltine or cocoa for 1 cup of milk
Only fresh fruit may be eaten between meals

OMIT FROM THE DIET

Salted meats as	Highly seasoned foods	Miscellaneous
Bacon	Pepper	Tea
Smoked ham	Vinegar	Coffee
Corned beef	Spices	Rich gravies
Salted fish	Pickles	Rich pastries
Meat soups or	Catsup	
Meat broths		

Use peas baked beans lima beans and soy beans only occasionally

There are special dietary measures to be used especially when the kidney is failing to excrete the nitrogenous substances ade quately In the more advanced cases of chronic nephritis especially with nitrogen retention and hypertension the diet sug gested by Kempner may be used This diet provides an average intake of 250 to 350 gm of rice (dry weight) daily, which is either boiled or steamed in plain water, and fruit juice, without salt milk or fat

Iron therapy has been a stand by in the treatment of chronic nephritis as anemia is frequently present Iron and ammonium ci trate 10 grains (0 6 gm) three or four times a day has been a favorite for many years Vitamins occupy a questionable thera peutic position but as the general nutrition of the patient is usually undermined by ne phritis, some form of multiple vitamin therapy may be helpful

Regarding the treatment of the renal le sion itself, removal of a foci of infection must occupy a prominent place Diseased tonsils

infected sinuses and infected teeth may be the source of an infection which retards the healing process in the kidney Although once it sets in chronic nephritis rarely if ever heals completely it is important to remember that the course of chronic nephritis is characterized by periods of remissions and periods of activity It is the function of the physician in charge to bring about a remission in the inflammatory lesion of the kidney and to maintain this remission as long as is possible by exercising good clinical judgment and employing all the therapeutic measures at hand

Treatment of the Clinical Manifestations As a result of chronic glomerulonephritis certain clinical syndromes develop which require special treatment Chronic nephritis is characterized by the five main syndromes the urinary syndrome edema hypertension azotemia and uremia These syndromes may all occur at the same time and during the course of nephritis one or all of them may disappear for a time perhaps to return later or never to return At times in the course of nephritis hypertension and hematuria dominate the picture at other times edema will be the outstanding feature and azotemia and uremia usually terminate the course of chronic glomerulonephritis In

where

Hypertension indicates that the glomeruli of the kidney are involved A persistent hypert

and the symptoms which attend it occupies an important place in the therapy of nephritis The general management of the case requires close consideration of the diet of the weight and of the general nutrition of the body There are a few special measures which must be given consideration

As cardiac embarrassment is a sequel to hypertension all efforts must be made to protect the heart as fully as possible This is done by reducing physical and mental activity

procedure to reserve the use of digitalis until the heart shows evidence of embarrassment by enlargement dyspnea or edema In such cases digitoxin or its equivalent in doses of 0 2 mg may be given daily or as often as indicated Special measures such as potassium thiocyanate may be used if there is a severe hypertension and if headaches attend it However potassium thiocyanate is a drug which may bring about unfavorable toxic manifestations and it should be used only when other measures fail to bring relief If it is decided to use potassium thiocyanate 3 grains (0 2 gm) are given two or three times a day The administration of this drug must be guided by the level of the potassium thiocyanate in the blood The optimal level is 8 to 12 mg per cent and the determinations must be made at weekly or biweekly intervals When this drug is used it is best to add either rutin 20 mg three times a day or some preparation of vitamin C in doses of 25 to 50 mg three times a day Other drugs have been advocated such as theophylline and other members of the xanthine group

As chronic glomerulonephritis progresses azotemia or retention of nitrogenous products in the blood stream occurs The treatment of azotemia is as follows The fluid intake is increased to 4000 to 5000 cc a day or enough fluid is given to assure an adequate output of urine for the output of the nitrogenous substances is to a large extent dependent upon the output of urine Therefore the output of urine becomes one of the most important factors in the treatment of chronic nephritis The kind of fluid to be

the patient is vomiting and uremia becomes imminent then the question of intravenous fluid administration must be answered This will be taken up in the section on uremia

Azotemia depends on the functional capacity of the kidney The reduction of the protein in the diet to as low as 0 5 gm per kilogram of body weight not only takes a load off of the kidney itself but retards the development of azotemia

When azotemia is not corrected the natural sequence of events leads to uremia

FRANCIS D MURPHY

UREMIA

Uremia may be divided into two distinct forms although both of them frequently occur together (1) Genuine uremia which is the result of any disease which impairs the secretion of urine and leads to retention of the toxic substances of metabolism not only nephritis but obstructive uropathies may be responsible for this kind of uremia (2) Convulsive uremia in which convulsive seizures are the chief manifestation This type of uremia has nothing to do with the retention of nonprotein nitrogen but is most likely the result of increased cerebrospinal fluid pressure which in turn results from hypertension

Genuine Uremia Genuine uremia is commonly the result of chronic glomerulonephritis *in which the renal parenchyma is almost* completely destroyed The clinical features *of genuine uremia are practically the same* whether the uremia is the result of chronic nephritis polycystic kidney disease tuberculosis of the genito urinary tract or of any other cause As the result of these changes alterations in the chemical composition of the blood may occur and it is the management of these alterations which occupies our main attention in the treatment As the uremic state may develop and occur in various degrees of severity in the course of many disorders the discussion of the treatment must obviously be quite general There are however three principal factors which will receive emphasis here (1) reduction of the intake of protein by which an attempt is made to cut down the work of the kidney (2) *the attempts to promote* diuresis and thereby augment the output of urine which *in turn increases* output of nitrogenous substances (3) the control of the electrolyte imbalance and the relief of symptoms

The reduction of the intake of protein is accomplished by giving a diet of 0 5 to 0 6 gm of protein per kilogram of body weight There is not much evidence to believe that there is any significant difference between any of the protein foods whether eggs milk or white or red meat Such low protein diets are usually easy for the patient to follow after they have become accustomed *to it* although it is well to supplement such low protein diets with the proper *minerals* and *vitamins necessary for the case* The amount of salt that is given in the diet is about 2 gm a day unless *edema is present* In such cases the sodium intake is reduced further In case *the patient is vomiting however there may* be hypochloremia and the addition of sodium chloride to the diet makes the diet more palatable and may make the patient feel much better Often in uremia there occurs a phase known as the salt losing stage in which there may be a genuine hypochloremia This must be corrected by the addition of salt to the diet or by the administration of intravenous physiologic saline solution

It is important to increase the output of urine as the output of urea and the other toxic substances of metabolism depend on the urinary output This is accomplished by *giving 2000 to 4000 cc of fluid* a day *unless* there is some special contraindication to this *amount Heart failure constitutes the main* contraindication for large quantities of fluid

In uremia renal insufficiency is usually fairly well advanced and the use of the stronger mercurial diuretics is not indicated However aminophylline or other xanthine diuretics may be tried For example 7½ grains (0 5 gm) of aminophylline may be

salt type and the mercurials are contraindicated as they may promote an already impending acidosis *At times the urinary output* is dependent on the condition of the heart and *the general circulation Small doses of* digitalis may be used to improve the circula

In genuine uremia nausea vomiting and acidosis occur These require the use of intravenous solutions for the purpose of combating dehydration acidosis and *electrolyte* imbalances The question arises as to what kind of fluids and *how much is to be given* The answer may be stated in a practical way *There are four kinds of fluids in common* use (1) glucose solutions 5 10 and 50 per *cent* (2) physiologic salt solution (3) whole blood plasma and serum albumin (4) the alkaline solutions such as sodium bicarbon

ate, 7 5 per cent solution and ⅙ molar lactate solution In order to determine which fluid should be given, certain determinations of the blood must be made The quantity of blood urea nitrogen is determined as well as the quantity of albumin in the plasma, the CO_2 combining power, and the level of the sodium and chloride of the blood On these determinations one injects the fluid which is indicated For example, if there is a rising nonprotein nitrogen in the blood stream, 5 per cent solutions are given in doses of 2000 to 3000 cc a day in order to promote diu

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By determining the CO_2 combining power of the blood the presence of acidosis or alkalosis is decided In impending acidosis, which is the usual thing in uremia, 1000 cc of 5 per cent sodium bicarbonate may be given every day The remainder of the fluid requirement is made up by giving 5 or 10 per cent glucose solutions in adequate amounts By these measures electrolyte and acid base imbalances may be corrected It is always well to determine the plasma albumin content and if there is a deficiency, plasma albumin may be used to correct it

Nausea, vomiting, headache, delirium, and coma are common clinical features of uremia These may become very distressing and require skillful therapeutic management For the headache, compounds of acetylsalicylic acid, barbiturates, and codeine are usually sufficient Occasionally it is necessary to resort to pantopon or to morphine Chloral hydrate may have to be given by rectum, 60 grains (4 gm), in 4 ounces of water This may be repeated two or three times in a day For vomiting, sodium pentobarbital, 1½ to 3 grains (0 1 to 0 2 gm), or sodium amytal in the same dose may be given Occasionally venesection of 500 cc of blood may be beneficial especially if the hypertension is present The fluid may be replaced by physiologic saline or some other fluids If vomiting persists, a stomach tube may be passed and gastric lavage undertaken with sodium bicarbonate solution

Within recent years more radical measures than those given above have been brought into use for the treatment of uremia These measures may be summarized under the headings of peritoneal dialysis, intestinal lavage, and the use of the artificial kidney Peritoneal dialysis has recently been reintroduced by Seligman, Frank, and Fine This kind of treatment, although it is becoming widely accepted and is apparently quite useful, requires the careful consideration of many factors For example, the electrolyte balance must be precisely controlled and the danger of peritonitis kept in mind at all times This form of treatment should be reserved for cases of renal insufficiency in which there are good chances of reversing the renal disease in progress The results of intestinal lavage have not been as satisfactory as those obtained with peritoneal lavage

There is more than one solution recommended for peritoneal irrigation and they may be enumerated as follows Tyrode's solution (20 to 30 liters daily) to avoid plasma depletion of electrolytes, glucose to avoid acidosis, penicillin and sodium sulfadiazine to prevent infection, and heparin to inhibit fibrin deposition

The lavage consists of running in about 5 to 20 liters a day It is continued steadily if possible for several days or until the condition of the patient is satisfactory

Convulsive Uremia Convulsive uremia may occur in conjunction with genuine uremia or it may develop independent of genuine uremia It is the result not of retention of substances of a nitrogenous nature but is usually produced by hypertension, increased cerebrospinal fluid pressure, and is followed by convulsions In these cases it is important to control the twitching and convulsions because they may lead to cardiac failure, respiratory failure, or both Control of the convulsion may be attended by the use of magnesium sulfate This may be given intravenously, in 15 gram (1 gm), doses three or four times a day During the use of this substance the blood pressure and the respiratory rate must be watched closely If the respiratory rate falls to 12 or below per minute, calcium gluconate must be held in readiness and given intravenously in doses of 10 to 20 cc This offsets the detrimental action of the magnesium Sometimes it is necessary to sedate the patient by giving pantopon or one of the barbiturates

topon, ⅓ grain (020 gm), morphine, ¼ grain (015 *gm*), *with atropine,* $\frac{1}{100}$ grain (006 gm), may be repeated for the control of the twitching and the convulsion Chloral hydrate per rectum is an old standby *It* is given, 30 to 60 grain (2 to 4 gm), doses rectally, two or three times a day if necessary

In the past the removal of spinal fluid by *spinal puncture* has been recommended in these cases There is some danger, however, in such a procedure because with the release of fluid on the brain the *medulla oblongata* may become jammed in the foramen magnum resulting in respiratory paralysis and death Within recent years I have not used this measure The control of the convulsion *is exceptionally important* in the treatment of nephritis because, unlike genuine uremia, in convulsive uremia the patient may recover from the episode and live fairly comfortably for many years afterward

Extrarenal Uremia Extrarenal uremia is a condition commonly characterized by elevation of the blood nitrogen, dehydration, *hypochloremia, normal or low blood pres* sure, and oliguria which may progress to anuria This syndrome usually occurs in association with some primary disorder independent of the kidney or urinary tract, such as intestinal obstruction, excessive vomiting or diarrhea from any cause or any condition causing dehydration and elimination of *chlorides from the gastro intestinal tract*

In the treatment of extrarenal uremia there are two things to be considered correction of dehydration and restoration of the volume *and electrolyte composition of the blood to* normal and treatment of the shock like condition which has complicated the primary disease under consideration These conditions *must* be *reversed* before anything else is accomplished, although if the primary cause of the condition is known, such as bowel obstruction, it should be corrected as soon as possible

The fluid-electrolyte-protein composition of the blood is accomplished by the administration of the correct kind of fluid, the proper amount, and the optimal rate of administration Physiologic saline solution, 3000 to *4000 cc every day, restores the extracellular* electrolytes and water In the presence of acidosis, sodium bicarbonate or sodium lactate intravenously is beneficial, in alkalosis, normal saline or ammonium chloride (200

amino acids, blood *plasma, or both are given,* although if food is tolerated by the patient, small feedings consisting of liquid or semi solid carbohydrate food are advisable If nausea and vomiting persist, nothing should be *given by mouth as this serves to* accentuate the disorder

Shock, if present, must be combated, and blood transfusions usually are of value

FRANCIS D MURPHY

LIPOID NEPHROSIS

There is no unanimity of opinion regarding the nature of genuine lipoid nephrosis Most observers believe that lipoid nephrosis is, in fact, a stage or a phase of chronic glomerulonephritis Personal observations,

lipoid nephrosis is that many pa... chronic glomerulonephritis have the nephrotic syndrome which may appear almost identical with the syndrome of genuine lipoid nephrosis

For practical purposes, lipoid nephrosis is a disease of the tubular apparatus with little or no inflammatory involvement of the glomeruli Even though, as Bell emphasizes, *most cases of so-called "pure lipoid nephrosis" show some degree of glomerulitis, there* are many patients with such a minimal glomerular involvement that for all practical purposes it may be considered lipoid nephrosis

In lipoid nephrosis there are *four outstanding* abnormalities (1) an excessive loss of protein through the kidneys, (2) a reduction of the serum albumin, usually to 2 gm per cent or below, with the consequent re- ... (3) ... ster ... erial

in the urine which doubly retracts polarized light and gives to the disorder its name and one of its peculiar characteristics

As the cause of lipoid nephrosis is not known, the treatment must be empirical There are three therapeutic considerations

General Care The general care and the protection of the patient from infection, particularly pneumococcal infection which has been a common cause of death in these cases The patient should obtain almost complete rest, as exercise seems to augment the albuminuria and the edema

Diet The diet occupies a most important position and is based on the idea that albumin of the blood stream leaks away in the urine Attempts have been made to replenish the plasma albumin by a high protein diet of between 3 and 4 gm per kilogram of body weight In addition to this optimal amounts of carbohydrate and fat are also given Because of the hypercholesterolemia a diet low in cholesterol such as one avoiding eggs is indicated One of the defects with the high protein diet is that many patients find such a diet obnoxious Concerning other dietary factors, the sodium of the diet must be kept at a low level It is best to keep

certain amount of sodium intrinsically For practical purposes, then, it is best to call for a diet without added salt and request a diet made up of salt free butter and bread and desalted milk

Whether limitation of fluid is advantageous has not been completely decided For my own purposes, I allow an optimal amount of fluid a day about 1500 to 2500 cc which satisfies the patient's requirements Schemm and others use a greater amount of fluid, with an acid ash diet, in an attempt to eliminate the sodium ion as completely as possible Such a routine as Schemm has recommended has not been completely satisfactory in many cases of nephrosis However, it deserves further trial before it can be given full approval or condemnation

The use of intravenous amino acids has been recommended highly by some but my own experience with amino acids intravenously has not been gratifying Diuretics, such as urea, mercupurin ammonium chloride and the xanthines, have all been tried scores of times and have never found approval Most of these diuretics may be harmless, but the mercurials may be quite detrimental

Intravenous solutions of human serum albumin are advocated in 25 to 50 gm doses daily until a desired diuresis has occurred This is the best measure in increasing the colloidal osmotic pressure The use of other substances for the purpose, such as blood plasma, acacia, gelatin and globin, have their drawbacks Acacia has been accused of causing enlargement of the spleen and liver and of being more detrimental than beneficial Many have discontinued its use completely and have condemned it Globin may be used in 25 to 50 gm doses daily The reports with globin in lipoid nephrosis have been encouraging

Removal of Edematous Fluid The question of performing abdominal paracentesis for the ascites of nephrosis is often debated However, I am in favor of removing the ascites whenever the abdomen becomes tight and respirations are interfered with To me it always seems to indicate a lack of therapeutic skill when a patient is brought to necropsy with an abdomen distended with fluid and the chest so filled with fluid that the breathing space had been greatly reduced If abdominal paracentesis is done properly, few or no unfavorable reactions occur The danger of causing peritonitis in these cases is greatly reduced at the present time by the use of penicillin a day before and a day following the paracentesis

FRANCIS D MURPHY

LOWER NEPHRON NEPHROSIS

Lower nephron nephrosis is a disorder which has become widely known within recent years It is an acute condition characterized by the presence of lipoid vacuolization of the cells lining the ascending limbs of Henle's loop In the distal convoluted tubules and the collecting tubules, there is precipitation of pigment casts, and these changes are followed by necrosis and extensive degeneration of the epithelial cells of the entire lower nephron A corresponding clinical picture of severe oliguria or complete anuria, rise in the blood pressure, and an elevation of the nonprotein nitrogen of the blood is present Nausea, vomiting weakness, and collapse are also constant f

The lower nephron nephrosis may be produced by a variety of disorders. It may occur with the crush syndrome, the transfusion reaction, injuries of various kinds, trauma, abortions, burns, and sulfonamide intoxication as well as many other things. These clinical and pathologic complications give rise to many theoretical considerations in treatment.

At the present time there are many different therapeutic suggestions, but the following treatment seems to be the most practical.

As the chief clinical feature is oliguria or anuria and many of the other changes are dependent on this, immediate treatment is directed to relieving anuria. In this regard, many measures have been advanced, for example, splanchnicectomy as recommended by Trueta and associates, spinal anesthesia, roentgen irradiation over the kidneys, and decapsulation. Personal experience with lower nephron disease and anuria prompts me to advocate conservative measures, as follows:

(1) If the patient is in a state of collapse and shock, a transfusion or plasma transfusion must be given to control the shock.

(2) Administration of 1000 to 2000 cc. of 5 per cent glucose solution daily is indicated, and if diuresis sets in, the amount of injected fluid may be increased accordingly. If the patient vomits considerably, there may be hypochloremia and if so, a physiologic saline solution may be added to the daily injection of glucose solution.

(3) The CO_2 combining power of the blood is determined as well as the sodium and potassium levels. If there is an acidosis impending, then 5 per cent bicarbonate solutions or 1/6 molar lactate solutions should be given intravenously to control acidosis. Occasionally alkalosis may be present and if it is, 1000 cc. of a 1 per cent ammonium chloride solution may be given to offset the alkalosis.

(4) It is well to determine the plasma albumin content of the blood and add intravenous plasma albumin or plasma to elevate the plasma protein.

(5) *As the anuria in these cases* is associated with an increased blood volume, careful attention must be given to the heart, for circulatory failure with pulmonary edema may set in and terminate the patient's life. Because of this danger, one must be cautious of the amount of fluids administered intravenously for, as Strauss points out, many of these patients are *drowned with large volumes* of intravenous fluids. Early and slow digitalization is indicated in these cases but overdosage must be guarded against.

(6) When diuresis sets in, the amount of intravenous fluids may be increased and the levels of sodium, chloride, potassium, and plasma albumin must be watched closely and proper measures instituted to keep these elements at an optimal level.

Other measures which have been recommended include the intravenous use of 50 cc. of 50 per cent glucose with 7½ grains (0.5 gm.) of aminophylline, even though diuretics are not particularly advisable in the presence of anuria. Diathermy applied over the kidney area has been followed by fairly satisfactory results in some cases. Decapsulation has been recommended and some good results have been reported. It is not advisable to attempt decapsulation until about the seventh day of anuria, for until this time spontaneous diuresis may occur at any time. Although decapsulation has fallen into disrepute, it is recommended by some urologists.

It is in cases of acute toxic lower nephron nephrosis that the lesion of the kidney is considered to be reversible. Therefore, it is in these cases in which the artificial kidney and peritoneal and intestinal lavage have been advocated. These measures, however, are still in the stage of clinical investigation and are not ready for approval or for recommendation at the present time.

One of the prominent examples of lower nephron nephrosis is brought about by the *crush syndrome. This condition may be suspected* in a patient with a history of a crushed limb or occlusion of arterial supply for several hours. Upon restoration of the blood flow, the limb usually swells and becomes hard and paralyzed. At times shock occurs which is caused by fall in blood pressure and associated with hemoconcentration. Within the first 24 hours renal damage may not be exhibited, but if it does occur urinary output and specific gravity diminish and unless a large diuresis is established the patient may die from nitrogen and potassium retention.

In treating this condition the following

measures may be instituted (1) pressure bandaging of the injured limb, (2) the use of an alkali for control of an acid urine, (3) restoration of blood volume and blood pressure by controlling shock, (4) adequate fluid intake

The injured limb may be treated by means of a pressure bandage and kept cool to decrease the rate of autolysis and allow living tissue to survive on a smaller blood supply

An alkaline urine may be obtained by giving sodium bicarbonate or some other mild alkali, 60 grains (4 gm) hourly by mouth If vomiting is present 1 liter of isotonic sodium lactate given intravenously will produce the desired results If a diuresis cannot be obtained within 12 hours, despite alkali therapy, renal damage should be suspected and fluids and alkaline substances should be stopped as their use may bring about alkalosis which develops readily in patients with renal failure

By the transfusion of plasma and crystalloid solution such as saline or lactate, the fall of renal blood flow may be prevented Shock may be combated by the usual methods of transfusion of blood and plasma

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tions of the kidney is the elimination of the disorder in its early phase before the disease progresses and leads to total destruction of the renal tissue The removal of the obstruction and the institution of normal urinary drainage must be carried out by a competent urologist

and there are frequency, urgency, and dysuria The treatment may be divided into the general and the specific measures

General treatment consists of rest in bed, administration of large amounts of fluid, 3000 to 4000 cc a day and a carefully selected diet Furthermore, the dysuria and urgency, which may be intense, are often relieved by giving alkaline drugs as sodium acetate, sodium bicarbonate or sodium citrate These drugs alkalinize a highly acid urine and bring about relief Sodium citrate may be given, 60 grains (4 gm) every 24 hours and is safe in such doses even for children

PYELITIS AND PYELONEPHRITIS

Pyogenic infections of the kidney embrace pyelitis pyelonephritis, pyelonephrosis and infected hydronephrosis conditions that eventually destroy the kidney s function unless the inflammation is controlled Various organisms may be the cause of these pyogenic infections although *Bacillus coli* is considered the responsible one Staphylococcus or streptococcus however, may be the etiologic organism and *Bacillus proteus* may occur on rare occasions The treatment of these bacterial infections requires a close study of the urologic phases of the disease One has to determine if obstruction is present and what the nature of the obstruction is before proper treatment can be considered

No one method of treatment is suitable to every occasion In some cases the sulfa drugs or the antibiotics will bring about remarkable results while in other cases they may seem to be utterly useless The main problem in the management of these infec-

ment are as follows (1) the urinary antiseptics, (2) the sulfonamides, (3) penicillin, and (4) streptomycin

Hexamethylenamine and sodium acid phosphate are excellent urinary antiseptics and may be given in doses of 180 to 225 grains (12 0 to 15 0 gm) three times a day Antiseptics are useful for a mild pyelitis when the infection is of a low grade and the patient is not particularly ill The mandelic acid preparations such as ammonium mandelate or calcium mandelate may be given, 30 to 45 grain (2 to 3 gm), doses three or four times every day, i e , after meals These antiseptics however, may cause nausea and

ment of pyogenic kidney conditions for a number of years, and the results have been quite gratifying Numerous sulfonamide

compounds have been recommended for various kinds of infections of the kidney, but experience within recent years has shown that there is no great difference between various sulfonamides in respect to special action on certain bacteria nor is the reaction of the urine of any great significance in the therapeutics of these drugs

We must always remember that the sulfonamides may have a toxic action on the kidney They may cause obstruction in the renal pelvis by the presence of sulfonamide crystals, and thus bring about mechanical disorder in the kidney However, the sulfonamides may produce a nephrotoxic action on the kidney especially in the tubular apparatus where there may be necrosis and destruction of the epithelial cells of the lower convoluted tubules as well as the cells lining the loops of Henle Of course, other toxic manifestations occur such as anemia due to hemolysis of the red blood cells fever and skin eruptions may even produce dermatitis exfoliativa

The protection of the patient against the toxic reaction of the sulfonamides is accomplished by the use of large quantities of fluids when these compounds are given It has been shown by Murphy and Woods that the acetate derivatives are more soluble in *the alkaline than in the acid urine and it is* particularly valuable to keep the urine alkaline when one is administering sulfonamides for the special purpose of preventing renal [illegible] the drugs themselves In order [illegible] in divided doses

Sulfathiazole or sulfadiazine may be used in the same doses, 1 gm every 4 hours The most popular drug in urinary infections is sulfadiazine, if gram negative organisms are present, however, sulfathiazole is the sulfa drug of choice

Penicillin is excreted in the urine and is effective in certain types of bacterial infection of the kidney However, it is considered much less effective than sulfonamides in the treatment of the *Bacillus coli* infections When the infection is nonhemolytic streptococcal or staphylococcal, the use of penicillin is the therapy of choice, as these coccal infections are resistant to sulfonamides

The use of penicillin in the treatment of infections of the kidney requires a different standard of dosage than when penicillin is used in generalized septicemia When a blood culture is positive, the nature and sensitiveness of the organism to penicillin in vitro are of considerable importance in regulating the dosage The level of penicillin in the blood stream too becomes an important factor in treatment when there is generalized infection However, in the treatment of urinary tract infections such considerations are not significant The proper dosage however, is important, and 100 000 units of penicillin intramuscularly every 3 hours will usually bring about gratifying results If the fever and the infection persist after 3 or 4 days, the dose must be doubled

Penicillin has not the drawback of the sulfa drugs as toxic reactions are rare However, they do occur and therefore must be considered Skin eruptions, rashes and at times even dermatitis exfoliativa may develop When a skin irritation appears on the face, penicillin should be stopped as it is too dangerous to continue treatment when there is any evidence of intoxication

When penicillin and other measures fail to control the infections of the urinary tract streptomycin may be used While strepto*mycin has not been used long enough to* give final statements, it is helpful in the treatment of infections due to gram negative bacilli such as *Bacillus coli* However its chief value seems to be in *Proteus ammoniae* and *Aerobacter aerogenes* The dosage of streptomycin is 30 grams (2 gm) daily, divided into eight doses, for about one week Streptomycin produces its best results if the urine is kept alkaline, but this is not resorted to until necessary because of the unfavorable toxic reactions which may occur The toxic effects are similar to those of penicillin However, streptomycin may be followed by nerve deafness ataxia and dizziness, but these undesirable reactions usually clear up and are not permanent

When the kidney infection *is resistant to* the medical measures given above, lavage of the renal pelvis by a urologist is recommended (See note at end of section on Cystitis)

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CYSTITIS

Cystitis is a general term used to define any urinary tract infection in which there are bladder symptoms Treatment of this condition is secondary and of far less import than to determine the primary cause of the bladder inflammation and to treat it adequately. This cause frequently lies in the upper urinary tract

The treatment of cystitis itself may be classed into general and specific measures The general measures include bed rest, fluid intake, heat applied to the suprapubic area, sedation, alkalinization of the urine, and other symptomatic devices, specific measures consist of the use of chemotherapy, antibiotics, urinary antiseptics, arsenicals, and local measures directed to the bladder itself

Since cystitis is really a term which signifies a symptom complex, the physician s first duty is to relieve the condition causing distress to the patient In the acute stage of cystitis, bed rest is usually necessary and a liberal intake of fluids (enough to ensure an output of about 2 liters in 24 hours) is ordinarily quite important except in those cases where inflammation, extreme urgency, and frequency are present Fluids in these cases might lead to polyuria and an aggravation of symptoms

Heat applied to the suprapubic area or perineum, such as a hot-water bottle, hot rectal irrigation, or hot vaginal douches in the female, may also be of benefit The judicious use of barbiturates and codeine, 30 mg, or in severe cases, morphine, 15 mg may also bring symptomatic relief An old time remedy which is apparently effective, although it is not too rational, is the use of opium and belladonna suppositories rectally

Alkalinization of the urine may be accomplished by the use of potassium citrate, sodium bicarbonate, citrocarbonate, or any alkaline mineral water These alkalies, however, should be used only when they do not interfere with the chemotherapy given

Frequency and urgency may be reduced by one of the bladder antispasmodics, particularly tincture of Hyoscyamus, 30 minims three times a day, or tincture of belladonna, 10 to 15 minims three times a day In extreme frequency, the use of indwelling catheter drainage for a short period may be necessary, or if tenesmus and stranguria are severe, the installation in the bladder of one of the topical anesthetics, such as novocain or procaine, 4 to 5 per cent, may be helpful from the purely symptomatic point of view Free evacuation of the bowels is useful not only from the standpoint of making the patient more comfortable but also from that of reducing intestinal stasis which may be a factor in keeping the urinary tract infection alive or active

Cystoscopy in the acute stage is definitely contraindicated and should be done only under special conditions as the bladder is too inflamed and easily irritated The procedure is extremely painful in this condition and is another source of irritation that will cause the already existing pathology to flame up Catheterization should also be avoided

Before specific therapy is instituted in any urinary tract infection, one should obtain a culture of the urine to determine what the offending organism or organisms are Following this, either chemotherapy or antibiotic therapy is indicated

Of the sulfonamides, the most effective are sulfadiazine, sulfathiazole, or sulfamerazine A full systemic dose of these drugs, however, is not necessary, as in urinary tract infections usually 30 grains (2 gm), given in 0 5 gm doses four times a day is sufficient to achieve high levels in the urine Because of the small dose needed and because one always takes pains to assure a good urinary output, concomitant alkalinization of the urine is not necessary and crystalluria is seldom seen

Since the lower gastro intestinal tract is not an infrequent source of urinary tract infection, an attempt at sterilization of, or at least a reduction in, the bacterial flora, may be quite helpful This may be accomplished with one of the poorly absorbed sulfonamides such as sulfasuxidine, 180 grains (12 gm), daily or sulfathaladine, 60 to 90 grains (4 to 6 gm), a day

Penicillin, 20 000 or 30,000 units every 3 hours, or one of the slowly absorbed depository types of penicillin in a dosage of 200,000 to 300,000 units daily is helpful This is effective in most gram positive infections of the urinary tract, however, the

great majority of urinary infections are caused by gram negative organisms which are *resistant to penicillin*

Streptomycin is an exceedingly effective urinary tract antiseptic, perhaps the most *effective of all in that it is capable of eradicating* certain types of gram negative infections which are resistant to all other types *of therapy The dosage is 25 to 30 grains* (1 5 to 2 0 gm) daily The untoward reactions of this form of therapy, however, must be borne *in mind and its use should be* properly reserved for those cases which prove resistant to the other usual types of *treatment*

Mandelic acid and its derivatives are good urinary tract antiseptics in the treatment of *gram negative infections and in the treatment of Streptococcus faecalis* infections which are usually resistant to sulfonamide *therapy A urinary concentration approaching* 1 per cent is necessary before these antiseptics may be used This means that about *180 grains (12 gm) of the drug must be* given in 24 hours to achieve a sufficiently high concentration This is one of the few *instances in which one purposely produces* a diminished urinary output The urine during mandelic acid therapy must be kept at a pH between 5 and 5 5 and urinary acidifiers must be given to achieve this desired degree of acidity The use of mandelic acid should not be continued for more than 2 weeks as a clinical acidosis may result, nor should it be used in cases in which there is depressed renal function or in patients having gastro intestinal disturbances, as it is poorly tolerated However a mandelic acid derivative mandelamine, has been shown to be about as effective, and in smaller dosages without producing gastro intestinal intolerance Methenamine is one of the old urinary antiseptics and if used properly may be effective in doses of 75 to 150 grains (5 to 10 gm), in 24 hours associated with a urine acidifier, since this action depends upon the liberation of formaldehyde in the acid bladder urines

There is a rare type of urinary tract infection, frequently severe and frequently diagnosed as cystitis, in which no organism can be demonstrated (the so called sterile pyurias or amicrobic pyurias) In these inflammations a viral etiology has been suggested They are resistant to all the usual chemotherapeutic agents and antibiotics but respond dramatically to the arsenicals such as neoarsphenamine or mapharsen The arsenicals are also helpful in certain types of staphylococcal infections which prove resistant to other types of therapy

Local measures directed to the bladder are ordinarily not used during the acute stage but find their chief use in the treatment of *chronic urinary* tract infections This form of treatment includes irrigation of the bladder cavity itself by use of the various types *of irrigating solutions, such as* potassium permanganate, 1 5000 saturated solutions of boric acid normal saline, or acriflavine, 1 8000 *These irrigations are carried out* once or twice daily, about a liter of solution being used during the process When alka*line incrustations are part of the bladder,* their removal may usually be effected by dissolution with an acid irrigating solution *such as phosphoric acid, 0 5 to 1 per cent* acetic acid in the same concentration, or some of the buffer acid solutions such as Suby's solution (solution G or M) Silver nitrate solution in concentrations varying from 1 10 000 to 1 500, may be useful especially where bleeding is associated with the bladder inflammation

The only type of true primary cystitis is that called interstitial cystitis, panmural cystitis, or Hunner's ulcer This condition must be properly diagnosed by means of the typical history as well as the cystoscopic picture It is a chronic form of cystitis of rather infrequent occurrence Management is exceedingly difficult because of the chronicity of the condition and at times the extreme severity of the symptoms Many types of therapy have been advocated Careful bladder irrigations with or without benefit of anesthesia, and the use of increasing strengths of silver nitrate solution may be helpful at least temporarily There is *no* specific therapy since the exact etiology is unknown

Any acute cystitis which *responds poorly* or not at all to the usual measures after 2 weeks of therapy and all chronic cystitis must have *a thorough investigation* of the entire urinary tract, as a primary source will

unquestionably be found outside of the bladder *

FRANCIS D MURPHY

RENAL CALCULI

The management of both ureteral and renal calculi is usually the function of a trained urologist However, the treatment of the acute attack often must be carried out by the general practitioner or internist, as surgery is not indicated in the treatment of all cases of ureteral or renal stone

The size of the stone, its location, and the response to the infection by the use of drugs are factors which determine the mode of treatment to be carried out

In the treatment of the acute attack, morphine, ¼ grain (015 gm), and atropine, 1/100 grain (0006 gm), must be given rapidly, if necessary every one half to one hour, until the pain is relieved It is hardly worth while to temporize with other measures of palliation It should be realized, however, that under conditions of anuria, chills and fever, persistent costovertebral angle pain and tenderness, or persistent intractable pain, some type of drainage must be instituted as an emergency measure

In the period between the acute colicky attacks, measures must be used to clear up an associated infection and to bring about passage of the calculus The preparations used for the infection are those enumerated above in the discussion of the treatment of pyelitis—the sulfonamides, penicillin streptomycin, aureomycin, and chloromycetin

As urinary stones may be of different chemical mixtures, it is necessary to determine if possible the kind of stone present in order to prescribe a routine of diet and treatment They may include uric acid, calcium phosphate, cystine, or calcium oxylate stones Special studies of the urine and the blood are important in determining the nature of stones present As an example, high blood calcium, that is, above 11 mg per cent, is suggestive of hyperparathyroidism which may have to be treated specifically by removing tumors of the parathyroid glands The urinary pH most favorable for the dissolution of the kind of stone present is indicated One must provide for a fluid intake of from 4000 to 6000 cc a day as well as to employ the antibacterial agents necessary for the control of the infection If a small renal stone is passed, the nature of this stone should determine the subsequent routine to be prescribed for a patient in an effort to prevent the formation of other stones Large stones which obviously will not pass must be treated surgically

Where no specimen of stone is obtainable to determine its nature, the urinary pH and the consideration of infection as well as the kind of crystals in the urine may be helpful When the nature of the stone is known, such as carbonate or phosphate stones, the following formula has been recommended for dissolving the calculi This formula is known as solution G and is as follows

Citric acid (monohydrate)	32 25 gm
Magnesium oxide (anhydrous)	3 84 gm
Sodium carbonate (anhydrous)	4 37
Water ad	1000 cc

The formula is administered by means of ureteral catheterization

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* Aureomycin and chloromycetin are now known to be valuable agents in the treatment of urinary tract infections These drugs are of value against most of the usual bacterial invaders of the urinary tract except *B proteus* and *B pyocyaneus* The usual method of administration is 500 to 750 mg every 6 hours Polymyxin a new antibiotic, is effective against organisms of the Pseudomonas group which are not vulnerable to aureomycin or chloromycetin The specific dosage of polymyxin cannot be stated at the time of this writing—*Editor*

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CHAPTER XI

DISEASES OF THE LOCOMOTOR SYSTEM

RHEUMATOID ARTHRITIS

Diagnosis. Rheumatoid arthritis is a chronic, generally progressive disease, manifested primarily as a destructive and deforming articular inflammation Characteristic complications include subcutaneous nodules, nodular inflammation of muscles and nerves, ophthalmitis, anemia, vasomotor disturbances, muscular atrophy, loss of weight, hypertrophy of lymph nodes and, in some cases, a *chronic progressive inflammatory carditis* The disease occurs at all ages in children, in mature adults, and in the aged In most cases, however, it first appears between the ages of 20 and 40

The cause is unknown Search for the re

rected to the possibility of a hormonal etiology by discovering the efficacy of the adrenal cortical hormone, cortisone, 17-hy-

however, has not disclosed the etiology of rheumatoid arthritis, and the manner in which these substances, or some modification of them, will eventually be used for treatment remains to be established There is now reason to believe, however, that rheumatoid arthritis will become susceptible of effective control

Two major types of rheumatoid arthritis are encountered, but these are not always distinct and some individuals display a mixture of the two, with the clinical features of one or the other predominating In the first type, joints of the extremities are chiefly affected This variety may be designated the peripheral type A second variety affects the spine primarily and is variously designated as rheumatoid spondylitis, Marie-Strumpell disease, von Bechterew's disease, adolescent spondylitis, spondylitis deformans, etc The peripheral type predominates among females, its incidence being two to three times greater than in males The spinal variety, on the other hand, is most commonly encountered among males, its incidence being 10 to 20 times as great as among females

The usual mode of onset for both types is insidious although it may be precipitous *Ordinarily, patients observe stiffness and swelling* in several joints, complain of fatigue, loss of weight, and pain on motion Joints which are affected become visibly swollen, tender, and sometimes discolored Only a few scattered joints may be involved, but in the more typical cases multiple joints are attacked in a symmetrical pattern In its advanced stages, rheumatoid arthritis cannot readily be mistaken for any other disease, the patient presenting a picture of which the *predominant features are symmetrical articular swellings*, capsular contractures, flexion deformities, inanition, subcutaneous nodules, wasting of muscles, and various trophic skin disorders

Laboratory data may aid in establishing a diagnosis and may provide assistance in

is usually elevated and the globulin fraction of serum proteins is commonly increased relative to the albumin fraction, the albumin-globulin ratio being often reduced or actually "inverted in consequence Leukocyte counts generally are within normal limits although occasional variations are encountered Acute cases may show a leukocytosis of between 10,000 and 20,000 Rarely, in cases of long duration, the total leukocyte counts are low, ranging between 2000 and 4000 per cubic millimeter

In the earlier stages of rheumatoid ar-

thritis roentgenograms generally disclose swelling of soft tissues about joints and atrophy of subarticular epiphyseal bone In more advanced cases roentgenograms show narrowing of articular spaces and erosion and atrophy of articular cartilages In late stages erosions and destruction of epiphyseal bone may be seen

Treatment GENERAL COMMENTS Physicians approaching the problem of treatment for rheumatoid arthritis must take many factors into account It is essential first of all to realize that *no single remedy which is regularly effective is available at this time* Consequently treatment should be planned for each patient in the form of a program made up of many parts each directed toward a separate aspect of the disease The patient s economic status must be taken into consideration Ideal care might perhaps entail prolonged hospitalization with professional physical therapy supervision of diet and frequent laboratory controls Such ideal treatment is rarely available for a patient with rheumatoid arthritis and in consequence a physician must be willing to make an appropriate compromise Home measures of physical therapy often must be substituted for more elaborate professional treatments Home made splints and supports may have to serve in lieu of custom made ap [illegible] Exper [illegible] es of medical treat [illegible] ures which can be carried out largely by the patient with the aid of members of his family

Physicians should keep in mind also that the therapeutic program must be altered from time to time as the manifestations of the disease alter in a never ending variety At one period a patient may be completely helpless requiring constant nursing care During this period he may have intense pain and may require narcotics At another period he may have little in the way of constitutional disturbances and his articular disease may cause only minor inconvenience A program of treatment suited to the first situation will obviously not be appropriate for the second

An important aspect of treatment in this condition is the matter of informing the patient regarding the nature of his illness and the procedures which he should employ in its treatment Thoughtful discussions between patient and physician are of great value for this purpose These discussions should provide the physician with opportunity to stress the need for patience and perseverance with treatment measures and to stress the value of such perseverance in improving the outlook both as to eventual recovery and to the avoidance of deformities

In general the treatment of rheumatoid arthritis will be discussed on the following principles (1) rest and regulation of activities (2) physical therapy (3) occupational therapy and psychotherapy (4) rehabilitation (5) roentgen therapy (6) fever therapy (7) heliotherapy (8) vitamin therapy (9) foci of infection (10) chrysotherapy (11) general measures and (12) cortisone and ACTH Perhaps developments of the near future will alter this list notably but the time has not yet arrived when these measures can be effectively supplanted

REST Of these several procedures rest is perhaps the most important although its significance may be modified as increased experience is gained with pituitary and adrenal hormone therapy Until that experience has been accumulated however rest should not be neglected its value although *empiric is well established*

Prescription for rest should be given in detail Each patient presents an individual problem Some terribly debilitated and suffering with active articular inflammation require almost continuous rest in bed To prescribe complete rest for *all* patients however is unrealistic and unless such advice is accompanied by directions for regularly continued physical therapy the advice may prove harmful Patients in whom the disease is inactive may be permitted nearly a normal degree of activity Between these two extremes lies a program of rest applicable to cases of intermediate severity For the "average case" 10 hours of rest in bed at night and 2 or 3 hours of additional rest during the day generally will suffice In addition certain joints more acutely affected than others or threatened with contractures may require local aids to rest such as splints partial casts or other supports

In short rest should be employed for rheu

matoid arthritis just as one would employ this measure in treatment of other chronic diseases The design should be to encourage the natural healing processes Overemphasized rest may result in excessive muscular weakness favor the development of deformities from disuse and unnecessary undermining of the economic status of wage earners On the other hand underemphasis on rest may produce results which are equally undesirable For example some patients instructed to exercise lest the joints "lock" drive themselves in an attempt to maintain activity thus aggravating the exhaustion which usually accompanies the disease Others wiggle their joints constantly thus aggravating local inflammatory processes A proper degree of emphasis to place upon both rest and activity should be determined by the physician after consideration of the condition of each individual patient

PHYSICAL THERAPY Physical measures of value for most patients include applications of heat massage and exercise Details concerning the use of these procedures belong in textbooks on physical therapy rather than here but a few points are mentioned for general guidance

Heat Apparatus for applying heat must be adapted to each individual's situation Where electricity is not available patients can resort to warm tub baths hot compresses or the use of warmed bags of grain or salt Hot water bottles electric pads infra red bulbs or home made bakers are available to the average city dwelling patient

Infra red lamps are commonly used by patients to whom electric current is available They should be conveniently mounted on a stand and employed with a reflector similar to the type used in connection with photographic illumination Two hundred and fifty watt "mazda CX bulbs or 200 watt carbon filament bulbs are economical and convenient.

For heating larger areas with infra red radiation an inverted cradle like apparatus within which are supported incandescent bulbs is effective Such electric bakers are especially useful where the spine or lower extremities require treatment. Directions for making a satisfactory baker may be obtained from the Council on Physical Therapy of the American Medical Association

Warm paraffin can be conveniently employed for heating joints Four to 6 lbs of paraffin are placed in the top compartment of a double boiler and warmed to melting by heating water in the lower compartment In this manner the wax is protected against catching fire When melted the wax may be allowed to cool until a thin film forms on the surface Hands may then be dipped slowly in and out of the wax 10 or 12 times The glove of wax thus formed is then allowed to remain on the hands about 20 minutes after which it may be peeled off and returned to the pan for further use Warm liquefied wax may be painted on other joints with a paint brush

Massage The purposes of massage are maintenance of muscle tone prevention of muscle atrophy and alleviation of spasms and contractures In rheumatoid arthritis muscles about affected joints may be massaged daily A family member can be taught to give massage at home thus dispensing at least partially with the need for expensive professional massages However home physical therapy should be supplemented by professional treatments once or twice weekly if possible

Exercises Most physical therapists recommend a period of exercises following heating and massage These exercises should be appropriate to the situation presented by each individual patient In the case of joints which are extremely painful exercises must be performed gently perhaps with the assistance of a technician or trained member of the family If the joints are less painful exercises may be more active or may even be performed against resistance

Experience indicates that deformities and contractures may be minimized by a carefully planned program of physical therapy which includes exercises during which affected joints are moved through their full

cians who plan occupational therapy for arthritic patients Occupational activity should consist of work which is interesting the work chosen should entail articular and muscular movements calculated to maintain

and improve action of affected joints it should not be excessively tiring Occupational therapy which has been properly planned may serve as an important aid in ridding patients of feelings of helplessness and dependency

PSYCHOTHERAPY There is a place for psychotherapy in the treatment program of patients with rheumatoid arthritis but the value of this measure should not be exaggerated Patients with rheumatoid arthritis may suffer exacerbations coincident with or subsequent to unusual psychologic stresses Hence these should be avoided if possible One valuable and effective measure of psychotherapy for patients with rheumatoid arthritis is a well ordered therapeutic program prescribed by a physician whose manner indicates reasonable optimism and confidence

OCCUPATIONAL AND PHYSICAL REHABILITATION In the past little attention has been paid to this aspect of the treatment of patients with rheumatoid arthritis but there is a need for rehabilitation procedures in many instances A strong effort should be made to maintain or establish economic usefulness for each patient Occupations should be chosen to fit physical capacities Ideal employment should maintain earning capacity without requiring excessive physical exertion Patients with rheumatoid arthritis usually cooperate willingly in making such plans and often display a remarkable degree of hardihood, tolerating much pain and fatigue in order to stay on the job This praiseworthy tendency needs to be encouraged as much as possible but patients should not be encouraged to work at occupations which aggravate the disease by traumatizing inflamed joints

During World War II rehabilitation procedures were organized systematically for arthritic patients at the Army Rheumatism Center in Hot Springs Arkansas Included in that program were such activities as gardening calisthenics pursuance of constructive hobbies and classroom instruction in various subjects These procedures often aided effectively in re establishing employability of demoralized patients who had spent many months in military hospitals and it is reasonable to believe that activities such as were employed at the Army and Navy hospital can be adapted to nonmilitary medical centers

ROENTGEN THERAPY Treatment of rheumatoid arthritis of peripheral joints by x rays has been generally discarded because controlled studies have failed to demonstrate any significant improvement following its use On the other hand roentgen therapy is being widely used for rheumatoid spondylitis Recommended technics for treatment of spondylitis are given in later paragraphs

FEVER THERAPY The popularity of fever therapy for rheumatoid arthritis reached a peak in America during the middle 1930's but this measure now has few proponents

recommend brief periods of cabinet therapy in order to prepare patients for massage and exercises For this purpose the duration need not exceed 30 to 40 minutes and body temperature need not be elevated beyond 99 or 100° F

Fever therapy by means of intravenous typhoid vaccine therapy continues in use by many rheumatologists This procedure may occasionally be followed by notable subjective improvement The author continues to use typhoid vaccine therapy for patients with active rheumatoid arthritis when an excessive degree of debility or anemia is not present and when arteriosclerosis is not advanced

given at intervals of two or three times a week Courses may be repeated at intervals of 6 months to a year if the first trial results in some improvement The first injection of each course should consist of 10 000 000 or 20 000 000 organisms Thereafter the dose may be doubled for each subsequent injection The patient's temperature should be checked hourly during the postinjection period until fever has subsided Thirty milligrams of codeine may be given for severe headache or for unusual muscular or articular pain Fluids should be given freely during the period of fever and a nurse or members of the family should be prepared to sponge the skin if an undue elevation of temperature occurs Typhoid vaccine fever

therapy is safe if carried out in this fashion

HELIOTHERAPY No evidence has been produced to indicate that sun bathing can favorably influence the course of rheumatoid arthritis However sun bathing is well tolerated and there is little to be said against it Sun baths should not be used to the exclusion of other more rational forms of treatment

VITAMINS During the past two decades the potential value of vitamins as a treatment measure for rheumatoid arthritis was carefully explored In general this work resulted in negative conclusions At present most experienced rheumatologists have concluded that no definite therapeutic value has been proved for any vitamin which has been applied in the treatment of rheumatoid arthritis

THE MANAGEMENT OF FOCI OF INFECTION Although the theory that rheumatoid arthritis is caused by focal infection is being generally abandoned experienced rheumatologists still search for infected foci while examining patients with the disease This is generally done in the belief that infectious foci may lower healing powers or resistance Radical treatment of suspicious foci rarely results in spectacular improvement of rheumatoid arthritis therefore surgery for a suspected focus should be undertaken only if the operation can be accomplished without notable risk

Teeth In dealing with dental problems in patients with rheumatoid arthritis it is important to preserve adequate masticating surfaces so far as possible Useful teeth should therefore never be sacrificed on the basis of a mere suspicion Devitalized teeth are not always infected and should not be removed as a treatment measure for the arthritis Deep pockets of pyorrhea should receive local treatments aimed at preserving the life of adjoining teeth Teeth having definite periapical abscesses should be removed and fragments of dental roots which may have been left following previous faulty extractions should also be removed

Tonsils Tonsillectomy is a justifiable procedure in a patient with rheumatoid arthritis if the tonsils are grossly infected or if they have been the sites of repeated acute infections In a majority of the cases this problem does not arise today because the tonsils have usually been removed prior to onset of the arthritis

Sinuses Indications for the treatment of infected sinuses in arthritic patients are identical with those which obtain in nonarthritic patients Suppurating sinuses should be provided with adequate means of drainage but operations on sinuses should not be undertaken merely on the basis of "suspicious" or "cloudy appearances of sinuses in roentgenograms

Other Foci The *cervix* should be examined for evidences of infection in every female with rheumatoid arthritis local treatment should be instituted only if clear cut evidence of infection is encountered

Prostatic secretions obtained following massage should be examined in male patients who have an otherwise unexplained pyuria Secretions which show more than 15 or 20 pus cells in each high power microscopic field may indicate the presence of infection In such instances local treatment with massage may be given once or twice weekly together with occasional brief courses of penicillin or sulfonamides

Diseases of the *gallbladder appendix colon etc* are no more frequent in patients with rheumatoid arthritis than in nonarthritic patients When infection is detected treatment should be planned according to rules which apply in patients without rheumatoid arthritis

CHRYSOTHERAPY Treatment of rheumatoid arthritis with gold was introduced by European physicians in 1927 but in America little attention was given to this subject until nearly a decade later Since then gold has been used to an increasing extent by physicians in this country and during the past 5 years has largely supplanted the use of other injectable substances Although some careful students of rheumatic disease still insist that the beneficial value of gold has not been established those who hold this view are in the minority The practicability of its use has been increased by the discovery that BAL is an effective treatment for some of the toxic manifestations which may appear during chrysotherapy

Dissemination of information to laymen regarding toxicity of gold has been a source of difficulty in making use of this

This publicity has caused

sion among some patients and it is not uncommon now to encounter individuals seriously afflicted with rheumatoid arthritis who cannot be persuaded *to submit to gold* therapy because comments in the lay press have made them fearful of toxic reactions

Publicity which has been given to discovery of the anti arthritic effects of cortisone and the pituitary adrenocorticotropic

available are reluctant to begin a tedious course of injections with gold Until such time as these hormones become available in quantity and until their usefulness and limitations are more fully understood chryso therapy will continue to occupy an important place in the vigorous treatment of rheumatoid arthritis On that account its use will be discussed at some length

Choice of a Preparation The compounds of gold most frequently used in America are listed in Table I Colloidal suspensions once popular have largely been discarded in favor of more readily absorbable preparations soluble either in water or in oil No one preparation is demonstrably superior to any of the others which are commercially available at this time

Chemical Name	*Proprietary Name*	*Solubility in Water*	*Physical State*	*Gold Content (Per cent)*
Gold sodium thiosulfate	Sanochrysine	+	Aqueous solution	37
Gold sodium thiomalate	Myochrysine	+	Aqueous solution	50
Gold thio glucose	Solganal B oleosum	—	Oil suspension	50
Gold thioglycol anilide	Lauron	—	Oil suspension	54

Dosage and Methods of Administration All preparations should be given intramuscularly There is no justification for intravenous administration A regimen which is commonly used in the case of myochrysine and sanochrysine is as follows Beginning with 10 mg doses are increased progressively to 25 mg Injections should be given twice weekly rather than once and should be continued until the patient has received

following completion of the initial course

Relapses Follow up stud es of gold therapy have shown a high incidence of relapses (up to 75 per cent of the cases) Approximately 50 per cent of such relapses occur within the first year following treatment This high incidence may be less under the continued treatment described above than under the discontinuous treatments which were formerly employed Relapses do not always respond to further treatment with gold

Mode of Action The mechanism by which gold produces its supposed benefits in rheumatoid arthritis is unknown Gold salts possess bacteriostatic and chemotherapeutic properties against a number of micro organisms but the benefits resulting from gold therapy in rheumatoid arthritis can scarcely be related to these properties since the disease is not believed to be of bacterial origin An effect on some enzyme system has been considered but there is no proof of such an effect and no information to relate it to the relief of rheumatoid arthritis

Metabolism of Gold Salts Soluble compounds of gold are absorbed slowly from the site of their deposit in the muscles Small amounts appear in the plasma within a few hours after an injection and later may be found in almost every cell of the body The greatest concentrations appear in the liver spleen kidneys and skin Approximately 75 to 90 per cent of the amount which is excreted appears in the urine and the balance appears in the stools The excretion rate is slow and is continued for a long time some gold has been demonstrated in urine 13 months after administration of the drug and

in plasma 10 months following its administration

Results of Gold Therapy in Rheumatoid Arthritis Satisfactory and even impressive results have been claimed for gold therapy by many writers on the subject, although some others have found no evidence of its benefits In a recently published review on gold therapy, Sundelin noted improvement rates varying from 40 to 95 per cent among reports of 3 800 patients treated The median improvement rate was 81 per cent Regarding these reports, some critics of gold therapy have objected that such claims were unjustified because comparison was not always made with improvement rates in untreated cases This criticism cannot be wholly answered today because studies conducted thus far have not been sufficiently objective to satisfy rigid experimental requirements

Toxic Reactions to Gold Toxic reactions are not infrequent during gold therapy and must be given serious consideration by a physician who employs this treatment The risks of toxic reactions should be discussed with the patient, and where possible with other family members, so that all will understand and share with the doctor the responsibility for any untoward occurrence The incidence of all toxic reactions has been reported as varying from 21 to 88 per cent However, serious toxic reactions occurred in only 4 or 5 per cent of the author's series of patients who have been treated according to the plan outlined above Prior to 1942, fatalities reportedly occurred in approximately 1 in 200 to 1 in 300 patients This incidence may be lower now because of the effective use of BAL in treating serious toxic reactions to gold

The toxic manifestations most frequently encountered affect the skin and mucous membranes These may range from mild pruritus or minor stomatitis to an intense exfoliative dermatitis Hepatic and renal lesions, reactions affecting the nervous system (peripheral neuritis, encephalitis), and

lytic anemias have been most prominent

Little is known concerning the pathogenesis of these toxic reactions although it seems certain that these reactions reflect something other than simple intoxication with the gold metal Serious and even fatal reactions have followed administration of a few doses containing an amount of gold too small itself to provoke a toxic reaction

There is no sign on which we can rely as an indication of the approach of toxicity A drop in the platelet count to less than 75,000 per cubic millimeter of blood a lowering of leukocyte counts to less than 4,000 per cubic millimeter, a rise of eosinophil counts, the appearance of albumin or erythrocytes in the urine all of these may be danger signs and should be regarded as warnings In some instances, pruritus has preceded serious skin reactions The physician should stop gold therapy immediately on the appearance of any of these warning signals, but he should also bear in mind that important toxic manifestations may appear without any prelim-

should be given to use of BAL Mild symptoms which at first may be regarded as evidences of gold reactions sometimes disappear without special treatments

BAL (British anti lewisite, 2, 3, -dimercaptopropanol) which was developed in Great Britain during World War II as an antidote for arsenical gas burns, has proved its value in the treatment of poisoning by gold and other heavy metals Recent investigations have disclosed that gold, as well as

protein from these combinations, forming tight metal-BAL compounds which are inert The metal, thus rendered nontoxic, is excreted by the body at leisure

Examples of gold toxicity which have responded satisfactorily to BAL therapy include exfoliative dermatitis, thrombocytopenic purpura, granulopenia, stomatitis, conjunctivitis, and nephrosis

BAL is dispensed in a 10 per cent solution in peanut oil containing 20 per cent of benzyl benzoate It is administered intramuscularly, first at intervals of 4 to 6 hours for 1 or 2 days, subsequently twice daily for 6 or 8 days, then once daily until the last

evidences of toxic reaction have disappeared The *dose* is 2 5 mg (0 025 cc of the solution) for each kilogram of body weight In most instances toxic reactions have subsided within a week or 10 days under this treatment In some cases treatment has had to be continued for 2 or 3 weeks

This substance has itself been responsible for a notable incidence of toxic reactions These have included malaise nausea vomiting salivation lacrimation sensations of warmth and abdominal pain Injections are sometimes painful and local abscesses have been observed

In general a relatively great risk from gold intoxication justifies the slighter risk of tox[illegible] from BAL Ho[illegible]

reactions some of which clear spontaneously following discontinuation of gold therapy one may properly observe the patient closely for a few days and in this manner attempt to avoid the need for BAL If indications point to a progressive toxicity however BAL should be given without delay

[illegible]

complete blood counts once monthly are adequate for most patients Additional laboratory controls should be employed whenever a suspicion is aroused that some toxic effects may be developing

Tentative Conclusions Regarding Gold Therapy The position which gold therapy may eventually occupy in the field of rheumatism is uncertain The risks which accompany it though less by virtue of the discovery of BAL are still notable and therefore prudence dictates that gold should be used only by those who have facilities for repeated laboratory studies of blood and urine Occasional patients show striking improvement during treatment but the quality of this improvement cannot be compared in most instances to that which is encountered in patients who have acquired intercurrent jaundice or in women patients who have become pregnant Neither does the effect of gold compare with the immediate effects produced by cortisone and the pituitary adrenocorticotropic hormone However until the latter substances become more pl[illegible] tiful and until their long term use [illegible] been further explored the continued use [illegible] gold is justifiable Gold should not be u[illegible] as a therapy for any articular disease s[illegible] rheumatoid arthritis and possibly psoria[illegible] arthritis There is no justification for its [illegible] in osteo arthritis or in fibrositis

OTHER MEASURES *Dietotherapy* Pro[illegible] nents for special antiarthritis diets have be[illegible] singularly absent from the medical scene [illegible] recent years In most instances a well b[illegible] anced diet adequate in vitamins and co[illegible] taining sufficient bulk to combat constipatio[illegible] is all that is necessary In the case of p[illegible] tients who have lost considerable weig[illegible] various means may be attempted to increa[illegible] the caloric intake The addition of sm[illegible]

Patients who are overweight should be e[illegible] couraged to lose weight

Analgesics and Sedatives An importa[illegible] part of the treatment program for a patie[illegible] with rheumatoid arthritis is a proper pr[illegible] scription of analgesics Salicylates are ine[illegible] fective in relieving the fundamental proce[illegible] but nevertheless are usually effective ten[illegible] porarily for relieving stiffness and sorene[illegible] Most patients can secure comfort by takin[illegible] 10 or 15 grains (0 6 to 1 gm) of aspirin [illegible] the morning on arising and at intervals du[illegible] ing the day Untoward reactions to salicy[illegible] ates used in this manner are extremely rar[illegible] Some patients tolerate enteric coated sali[illegible] ylate tablets better than uncoated tablets

Small doses of barbiturates for exampl[illegible] phenobarbital in doses of ½ grain (30 mg) t[illegible] 1½ grains (90 mg) are useful in allayin[illegible] restlessness and aiding sleep

Narcotics are needed occasionally whe[illegible] pain is severe as during an acute exacerba[illegible] tion or following some unusual traumati[illegible] episode For such instances codeine 30 mg[illegible] or demerol 100 mg may properly be used[illegible] It is vitally important for the physician t[illegible] keep in mind however that rheumatoi[illegible] arthritis is essentially a chronic disease an[illegible] that administration of narcotics is always at[illegible] tended by a possibility of addiction It i[illegible] better for the patient to submit himself t[illegible] discomfort from articular pain than to run this risk of narcotic addiction

Orthopedic Measures. This paragraph might properly be an extensive one including a review of operative and nonoperative measures which are of use in overcoming deformities and in maintaining mobility of affected joints The nature of this section, however, does not permit detailed treatment of this subject and therefore only a few principles will be mentioned Joints should be maintained in optimal positions by exercises, careful manipulations, by use of pillows, plaster supports, light weight splints, and simple traction apparatus when indicated In chronic stages of the disease, the experienced orthopedist may provide valuable aid by arthroplasties, arthrodeses, synovectomies, and occasionally by osteotomies In many instances, the patient s interests are best served when his treatment is directed both by an internist and an orthopedic surgeon

CORTISONE (COMPOUND E) AND PITUITARY ADRENOCORTICOTROPIC HORMONE IN RHEUMA- [illegible]

[illegible] treatment of rheumatoid arthritis is in prog ress Much of this work is still incomplete and many questions regarding proper use of both compounds, and especially regarding long term effects, are still unanswered How ever, both products are now available for use by physicians in many parts of the country [illegible]

treatments

Administration of both cortisone and of pituitary corticotropin results in almost every instance in a lessening of symptoms and in an improvement of articular swelling and tenderness Systemic manifestations tend to abate under the influence of these hormones In a majority of the cases, these benefits are apparent only during periods when admin istration is continued and regression usually occurs within a few hours or days after treatments are discontinued It has become apparent, therefore, at least in relation to rheumatoid arthritis, that cortisone or corticotropin treatments must be continued for [illegible]

longed use of these products is not sufficient to provide complete reassurance as to the safety of these long term measures It has been determined, however, that in most cases patients tolerate these hormones reasonably well for periods of 4 to 6 months

The degree to which an individual patient may show improvement with cortisone or with corticotropin depends in part on the duration of his illness before beginning treat ment Also important for determining the outcome is the factor of intensity of the articular and systemic manifestations Patients in whom symptoms have been present for periods up to 6 months or even for as much as a year, may show remarkable im provement immediately following the beginning of cortisone or corticotropin treat ment In such instances, pain and swelling may be almost entirely relieved and a sense of well being may be greatly augmented In more advanced cases results of treatment are determined largely by the severity of articular destruction present at the beginning of therapy In cases where joints have been extensively damaged, functional improvement may be slight or even insignificant, deformities of advanced degree are not overcome, subluxations are not altered, and ankyloses are not relieved In the most severe and advanced phases of the disease, in the so-called arthritic "derelict," recognizable benefits from the use of cortisone may be confined to an improved sense of well being, [illegible]

the following plan for dosage schedules has been followed in preliminary experiments Maximal daily doses of 100 mg have been found sufficient for adults with rheumatoid arthritis This amount should not, in general, be exceeded In treating children, the amount of cortisone needed to control symptoms of [illegible]

effective in providing reasonably satisfactory control of symptoms

As regards cortisone, satisfactory effects have been achieved by means of single daily doses The product available at present should be administered intramuscularly al though it is anticipated that oral administra

tion of cortisone will be feasible in the future

In order to provide a period for metabolic recuperation injections of cortisone may be given on 6 days of each week and injections may be omitted for several (3 to 7) consecutive days once monthly Results obtained by administering cortisone on alternate days and by administering alternating larger and smaller doses have not yet been thoroughly explored but appear to be inferior to results with more uniform daily treatment

(2) Pituitary Corticotropin Duration of the action of pituitary corticotropin available today is brief generally in the neighborhood of 6 to 8 hours Hence it is advisable in using this product to divide the daily dose *into three or four portions* and to administer these at intervals of 6 or 8 hours Potency of the products presently available is not always uniform but most patients respond satisfactorily to amounts ranging between 60 and 80 mg daily For children amounts required are proportionately smaller A satisfactory rule to determine dosage for children is to *start with a daily amount equivalent to 1 mg* per kilogram of body weight increasing or decreasing this amount as indicated by the response of the individual

Pituitary corticotropin available at present should be administered intramuscularly

Hyperadrenalism (Cushing s Syndrome) from Cortisone and Corticotropin Treatment of Rheumatoid Arthritis Prolonged administration of either cortisone or corticotropin in large amounts may induce in some sensitive individuals symptoms of hyperfunctioning of the adrenal cortex The resulting illness is similar to that which is seen with the spontaneously occurring Cushing s syndrome Earliest evidence of this effect is rounding of the face with production of an appearance which has been designated moon face A degree of edema of the lower extremities has been observed together with an acne form eruption on the face neck and back subcutaneous ecchymoses feeling of fatigue and even mental depression These symptoms should be searched for constantly during treatment with cortisone or corticotropin and their appearance should indicate a need for at least temporary cessation of treatment

Arterial hypertension has not appeared in patients previously normotensive and patients with moderate degrees of arterial hypertension have been able to tolerate treat

as this condition is invariably aggravated by cortisone or corticotropin treatment It is not yet known whether diabetes mellitus should be considered a complete contraindication to use of these hormones however as it may be *possible by employment of insulin* and proper diet measures to avoid serious difficulties in such cases while at the same time providing relief from symptoms of rheumatoid arthritis

Rarely intense nervous excitement has been observed following the use of both compounds and in some instances this symptom has progressed to a condition of outspoken psychotic behavior It is urgently recommended therefore that every patient who is receiving cortisone or corticotropin treatment be observed closely for signs of such abnormal behavior Treatments should be discontinued immediately when there is a *suspicion that unusual nervous tension is being produced*

Cortisone and Pituitary Corticotropin in Treatment of Juvenile Rheumatoid Arthritis (Still s Disease) Patients with juvenile rheumatoid arthritis respond to treatment with these compounds similarly to adults Signs of hyperadrenalism have been observed in children receiving this type of treatment and precautions regarding dosage schedules should be employed as outlined for the treatment of adults

Rheumatoid Spondylitis Results with rheumatoid spondylitis have been comparable to those seen in rheumatoid arthritis of peripheral joints Dosage schedules required are similar to those for rheumatoid arthritis of peripheral joints

Rheumatoid Arthritis with Psoriasis and Psoriatic Arthritis Patients with these conditions have responded similarly to patients with rheumatoid arthritis of the classic form not accompanied by psoriasis Partial or complete clearing of both arthritis and psoriasis has generally been observed in such cases

Rheumatoid Spondylitis The general principles which govern treatment of rheumatoid arthritis affecting peripheral joints

are applicable also to treatment of rheumatoid spondylitis Some special procedures for this disease require additional comment

Measures for the prevention and correction of the special deformities which occur in rheumatoid spondylitis should be advised in every case Among the instructions to such patients postural and deep breathing exercises should be stressed Where deformity has developed and the patient is stooped, efforts should be directed toward regaining lost height by stretching exercises and physical therapy procedures

ROENTGEN THERAPY Although roentgen treatment for rheumatoid arthritis of peripheral joints has been abandoned by almost unanimous consent, there is still some enthusiasm for this treatment in connection with rheumatoid arthritis of the spine Some patients report a lessening of pain tenderness, and subjective stiffness, and show an increase in chest expansion after x ray treatments At least, this treatment does no harm when carefully administered There is a risk of inducing sterility in young women by such therapy and this possibility must be given careful consideration in every instance when treatment is being planned for a female patient If a woman may eventually desire to have children, it is best to avoid this therapy

A technic for roentgen therapy of rheumatoid spondylitis widely used today is as follows 200 kilovolts with 0 5 mm of copper and 1 mm of aluminum filtration, a half-value layer of 0 9 mm of copper and a 50 cm skin target distance with an output of 50 r measured in air per field (usual size of field 200 to 300 sq cm) Each portion of the spine treated can be given 600 roentgen units Following completion of a treatment course, the process can be repeated once or twice if recrudescences occur and if the initial treatment has been productive of any promising results

CHRYSOTHERAPY Most American rheumatologists have abandoned gold therapy as useless in the case of spondylitis

EDWARD F ROSENBERG

REFERENCE

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OSTEO ARTHRITIS

The term osteo arthritis has numerous [illegible]

varieties are encountered, the primary and secondary The first, or primary, type is a distinctive clinical entity, an articular disease characteristically found in persons of advancing years, affecting certain joints and avoiding others, and having an extremely slow but progressive course Primary osteoarthritis is not generally associated with marked evidences of constitutional involvement such as anemia, fever, or loss of weight Secondary osteo arthritis is not a disease entity Rather, it is a painful condition associated with a series of pathologic changes similar to those found in primary osteoarthritis, but supervening on a primary joint injury which has been brought about by other causes Thus, joints which have been injured by trauma, infections, or by other articular diseases such as rheumatoid arthritis, may eventually show changes similar in character to those found in primary osteo arthritis, and may then be said to be sites of secondary osteo arthritis

In both types, characteristic symptoms are pain on use, muscular and articular stiffness, creaking and grating Effusions are uncommon except following accidental trauma Affected joints may become enlarged by marginal hypertrophy but not by inflammatory exudates Atrophy of adjacent musculature is not prominent

Joints most frequently affected in primary osteo arthritis are terminal interphalangeal joints of the hands (Heberden's nodes), knees, cervical and lumbar spine, hips (malum coxae senilis), metatarsophalangeal joints of great toes, temporomandibular joints (Costen's syndrome), and acromioclavicular joints Occasionally the middle row of [illegible] affected. [illegible] carpus, [illegible] are practically never involved in this disease

Laboratory data yield negative information in most instances of osteo arthritis

Sedimentation rates hemoglobin values erythrocyte counts and various blood chemical determinations are generally normal in uncomplicated cases Roentgenograms characteristically show narrowing of articular spaces various degrees of spur formations sclerosis of subchondral bone plates and occasionally subchondral cysts Osteoporosis is not a feature in usual cases

Secondary osteo arthritis *does not choose* any special joints but appears wherever concomitant factors of previous injury and continued use are present Secondary osteo arthritis is a localized disease

Treatment Treatment for osteo arthritis should aim to alleviate symptoms and prevent progression of the underlying pathologic processes Healing of this disease cannot be achieved because of the inability of cartilage to regenerate and because hypertrophied bone margins do not reabsorb

Useful measures of treatment for osteo arthritis include proper reassurance rest and physical therapy removal of traumatizing factors *orthopedic procedures* and medications Roentgen therapy removal of infectious foci gold therapy and hormones have not been proved of value

Reassurance Reassurance is a most important therapeutic measure for this condition Because symptoms of osteo arthritis often resemble those of rheumatoid arthritis these individuals commonly assume they are suffering from the more crippling rheumatoid arthritis This misconception is a cause *for great anxiety in many instances* and such anxiety should be relieved by thoughtful discussions between patient and physician

Rest and Physical Therapy Progression of the pathologic phenomena resulting from use and wear can be slowed by placing affected joints at rest Two to 3 weeks of rest in bed may result in long lasting alleviation of pain in severe cases Regulated periods of rest should be planned for each day Work and traveling activities should be thoughtfully examined with a view to minimizing trauma Unnecessary weight bearing should be eliminated Obesity should be overcome with diet. Abnormal postures should be corrected with well fitted supportive corsets corrective shoes or other orthopedic appliances

Measures of physical therapy worthy of use in osteo arthritis include applications of heat and massage These regularly provide a degree of comfort although no healing effect can be demonstrated Warm baths hot water bottles infra red bulbs and hot compresses serve satisfactorily as sources of heat Massages should be given preferably by a family member who can administer the treatments daily

Exercises have no place in the treatment of osteo arthritis Associated pathologic processes do not lead to ankyloses hence there is no need for movements to prevent fusion of joints Manipulations and exercises of all types may in fact hurry the wearing processes hence should be avoided

Orthopedic procedures useful for osteo arthritis are mentioned below in connection with measures for treatment of special forms of osteo arthritis

Medications Up to the present no definitive drug therapy for osteo arthritis has been evolved Useful medicaments however are those which relieve pain or aid in securing *rest through mild sedation Aspirin 0 6 gm* or sodium salicylate 0 6 gm provide comforting relief from pain in most instances although occasionally severe pain may require small doses of codeine or another narcotic

Thyroid extract vitamins iodides and colchicine are worthless

Diet Food factors beneficial for osteo arthritis have not been discovered Weight reduction diets are commonly employed for obese patients with a view to relieving the factor of excess weight

Roentgen Therapy Although roentgen therapy is often employed in centers where *appropriate apparatus is available* this form *of treatment is not of proved value* for osteo arthritis Such treatments are usually rela

[illegible]

intra articular injection therapies ot osteo arthritis have been recorded Acid potassium phosphate lactic acid and benzyl salicylate have been recommended currently for intra articular injections but none of these has found general acceptance

Hormones Both male and female sex hormones have been studied as treatment measures for osteo arthritis but none has stood

the test of time Their use cannot now be justified for osteo arthritis Cortisone and pituitary adrenocorticotropin have not yet been studied as treatment measures for osteo arthritis

Treatment of Special Forms of Osteo arthritis TERMINAL INTERPHALANGEAL JOINTS (HEBERDEN'S NODES) This most common of all forms of osteo arthritis is often asymptomatic but may cause aching burning numbness and stinging

Paraffin dips (see treatment of rheumatoid arthritis) and contrast baths are forms of physical therapy which can be readily employed in the home for Heberden s nodes This condition causes less discomfort if the patient avoids sewing and other handicrafts Eventually Heberden s nodes become painless and require no further treatment

CERVICAL SPINE Heat and massage with traction often provide notable relief Radiant heat first should be applied for 30 minutes followed by massage of the neck and shoulders Traction should then be applied to the head by means of canvas sling attached under the chin and occiput leading thence to a 4 to 6 pound weight suspended over the head of the bed This procedure may be carried out once or twice daily Patients with cervical osteo arthritis derive comfort from sleeping without pillows or with a single small pillow A padded cotton bandage 4 inches in width and 2 or 3 yards in length wrapped around the neck at night for periods of an hour or two several times during the day may also provide comfort by minimizing irritative effects of constant motions

LUMBAR OSTEO ARTHRITIS This condition may be associated with persistent lumbar backache or with repeated episodes of acute unilateral or bilateral lumbar pain In some cases the patients suffer episodes of sciatica Therapy during acute attacks should include rest if possible in bed on a firm mattress together with applications of heat and massages In some instances pain may be so severe as to require temporary use of narcotics

For more chronic symptoms of lumbar osteo arthritis supportive corsets or braces may aid in minimizing movements which aggravate symptoms Special attention should be given to regulation of occupational and recreational activities of patients with this condition as in some cases comfort can be maintained only by means of a restricted life program

OSTEO ARTHRITIS OF THE HIP This condition is generally encountered in middle aged or older patients Damage is commonly more advanced on one side than on the other but some patients have severe bilateral destruction The problem of therapy is a difficult one For severely painful episodes bed rest for a period of 2 or 3 weeks

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tion should be advised to seek occupations which permit their being seated for most of the day For severe cases effects of weight bearing should be minimized with canes or crutches

A surgical procedure worthy of consideration for some patients with osteo arthritis of the hips is cup arthroplasty This operation involves reshaping of the femoral head and acetabular cavity followed by interposition of a metallic cup between the femur and acetabulum The procedure is a major one and should not be undertaken in persons of advanced years with severe arteriosclerosis or other debilitating ailments

Lesser operations including forage or drilling of the femoral neck transplantation of the trochanters and cheilectomy (removal of spurs) have not proved to be of sufficient value to justify their regular employment Resection of the obturator nerve is still under study

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PALINDROMIC RHEUMATISM

The term "palindromic" derived from Greek roots meaning "to recur" was employed by Hippocrates to characterize erysipelas and other ailments tending to appear repeatedly in the same individual This term was applied recently to a "new previously unrecognized rheumatic disease the outstanding symptom of which is multiple recurring attacks of painful inflammation affecting joints and adjacent tissues

In this disease articular attacks usually affect but one joint although in some individuals a number of joints are attacked

simultaneously Episodes appear suddenly persist but a few hours or days and disappear leaving no residual articular damage Recurrences may be experienced at irregular intervals Fewer than 100 cases have been reported to this time

Onset of the attacks may occur at any time of the day but there is a tendency for attacks to have their onset in the late afternoon Attacks sometimes appear instantaneously the overlying skin becoming suddenly distended tender and discolored Attacks may be associated with considerable disability from pain but generally little or no constitutional reaction is evident Patients do not lose weight and generally show no elevation of the sedimentation rate Fever is not a feature of the disease

In addition to involving the joints some attacks affect periarticular structures and structures which are far removed from joints

A distinctive type of intracutaneous or subcutaneous nodule occurs in palindromic rheumatism These appear suddenly generally about the hands or fingers last from a few days to 6 or 7 days and disappear completely

Roentgenographic findings in joints are characteristically normal although patients with palindromic rheumatism may show changes from other causes as for example from unrelated primary or traumatic osteoarthritis

Treatment A physician who undertakes the treatment of a patient with this bizarre disease should understand that many questions concerning it remain unanswered The some metabolic factor Remedies already tried without success include measures against allergy psychotherapy anti infectious therapy and nonspecific shock therapy Histamine desensitization epinephrine ephedrine benzedrine and the newer anti allergic drugs including benadryl and pyribenzamine have been ineffective in palindromic rheumatism Measures directed against supposed infections including removal of foci and the administration of sulfanilamide penicillin and other antibiotics have also failed

Some patients have reported relief from miscellaneous measures but it is not certain that improvement which they noted was always related to the treatments which were being applied For example patients have claimed relief after receiving intravenous calcium gluconate and also after institution of such psychotherapeutic measures as adopting a child or taking a vacation

Several patients with palindromic rheumatism have recently been treated with soluble gold compounds This treatment was followed by a complete arrest of articular manifestations in each of 3 patients whose cases were reported by Boland and Headley This means of treatment should be investigated further

Patients with palindromic rheumatism should be examined carefully for infected foci and if any are present they should be removed General hygienic measures should be employed including regulated rest a carefully planned well rounded diet Simplified physical therapy measures should be used d moist lamps reg ons Analgesics drugs and sedatives should be administered for severe pain Unfavorable psychologic situations should be corrected wherever possible A search should be made for decided allergies and if any are found measures for their correction or elimination should be applied

If attacks persist and cause notable discomfort or disability gold therapy may be tried employing principles outlined for use of gold in the section on rheumatoid arthritis

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ARTICULAR DISEASES ASSOCIATED WITH SPECIFIC INFECTIONS

Acute suppurative arthritis results from metastasis of blood borne infections from extension of infection to joints from adjoining osteomyelitis or from penetrating wounds which enter articular cavities. Treatment of patients with such bacterial infections in

joints is today often the responsibility of the internist as well as of the orthopedic surgeon

From a numerical point of view, specific forms of arthritis constitute only a small proportion of "run of the mill' rheumatism cases Most commonly encountered among these cases are gonorrheal arthritis, tuberculous arthritis and arthritis associated with streptococcal and staphylococcal infections Syphilis, pneumococcal infections, meningitis, brucellosis, typhoid fever, and many other systemic infections are also occasionally responsible Infections with yeast or mold like organisms, including actinomycosis, blastomycosis, coccidioidomycosis, and histoplasmosis, are also occasionally encountered

Pains in joints, or arthralgias (not actual bacterial invasion or arthritis) may accompany many infectious ailments In such cases, the patients experience articular and muscular pains but suppuration does not occur Diphtheria, influenza, smallpox, mumps, scarlet fever, measles, tularemia, and many other infectious ailments may be accompanied by such arthralgias In such cases treatment should be directed against the underlying disease and special consideration will not be given to these problems in the present chapter

Treatments for specific forms of arthritis differ, depending on the organism which is responsible in any given case Only a few can receive comment here

Gonorrheal Arthritis Among specific forms of arthritis, gonorrheal infections still occupy an important place although this complication of gonorrhea has been decreasing steadily since the use of antibacterial drugs has become widespread

When a diagnosis of gonorrheal arthritis has been correctly made, the arthritis may be expected to subside promptly after treatment with adequate doses of penicillin A failure of penicillin therapy in a supposed case of gonorrheal arthritis generally reflects a mistaken diagnosis

In addition to treatment with penicillin bed rest, immobilization of acutely painful joints by splints or sandbags use of analgesics and narcotics should also be employed as needed

Daily intramuscular injections of 300,000 units of penicillin will generally suffice The intra articular administration of penicillin is not necessary in most instances

If suppuration has taken place in an affected joint, single or repeated aspirations may be performed to remove pus and thus lessen lytic effects on cartilage of enzymes

orrheal infections In mild cases, activity may be permitted as soon as the local and systemic evidences of infection have subsided After severe attacks, especially when purulent exudates have been in contact with articular structures for some days, weight bearing should be delayed for 10 days to 2 weeks after subsidence of the local symptoms in order to permit "hardening' of the cartilages

Tuberculous Arthritis The problem of therapy for tuberculous arthritis is a complex one, involving many factors Important for consideration are the age of the patient, degree of closure of epiphyses adjacent to affected joints, location and extent of tuberculosis in other structures, and general condition of the patient In most such cases, proper treatment requires combined efforts of orthopedists and internists Systemic therapy, orthopedic fixations—internal or external—and recently, streptomycin therapy constitute the categories of treatment methods to be employed

Rest in bed, high caloric diets, and heliotherapy are useful for most patients with tuberculous arthritis Orthopedic procedures applicable to articular tuberculosis vary with the site of the lesion and are not considered here

The role which presently available antibiotic substances may play in treatment of articular tuberculosis is not yet clearly established Penicillin and the chemotherapeutic drugs are without effect Earlier reports concerning effectiveness of streptomycin were pessimistic but more satisfactory results have been reported within the past year A favorable influence on the course of tuberculous arthritis has followed use of this substance in doses of 1 gm every 8 to 12 hours for 3 to 4 months Toxic reactions rarely interfered with continuation of this therapy More time will be required before

streptomycin therapy for tuberculous arthritis can be evaluated satisfactorily

Arthritis from Streptococcal or Staphylococcal Infections Infection with these organisms must be considered in the differential diagnosis in every case wherein acute articular inflammation is present Among patients with suppurative arthritis, staphylococci have been found responsible in approximately 50 per cent of the cases, hemolytic streptococci in 25 per cent, and miscellaneous other organisms in the remainder

Prompt and complete evacuation of infective effusions by repeated aspirations and lavage, or by means of incisions and drainage was the aim of treatment in these cases only a decade ago Following such treatments the incidence of ankylosis and the mortality rates were high Today ideal treatment consists of prompt bacteriologic diagnosis followed by administration of appropriate antibiotics These measures should be supplemented by arthrotomies only if destruction is proceeding in spite of adequate antibacterial therapy

Choice of antibacterial drugs can best be made after an accurate identification of the invading organism and where possible, after performance of appropriate antibiotic sensitivity tests Most strains of streptococci staphylococci pneumococci and members of the Clostridium family are susceptible to penicillin Also susceptible to penicillin are most strains of meningococci, gonococci, diphtheria organisms *Streptobacillus moniliformis* and *Spirillum minus*, *Treponema pallidum* and *Treponema pertenue*

For infections with gram negative bacilli streptomycin is preferable Usually sensitive to streptomycin are organisms of the Escherichia, Proteus Pseudomonas, Shigella, Pasteurella Klebsiella, and *Hemophilus influenzae* groups

Aureomycin and chloromycetin are effective against rather wide ranges of bacterial varieties, including some which are penicillin or streptomycin resistant Reports of the use of these newer agents in articular infections have not been published however, their employment would seem reasonable for patients in whom an organism resistant to streptomycin and to penicillin is causing the infection

Arthritis of Actinomycosis This condition generally affects the vertebrae, is often associated with formation of discharging sinuses and may readily be mistaken for tuberculosis Therapy thus far devised has been ineffectual and the mortality rate has been high Sulfanilamide, iodides, roentgen rays, and penicillin have been employed without notable success

Coccidioidal Arthritis Arthritis occurs both in the early acute or benign phases of coccidioidal infection and in the later chronic granulomatous phase of this disease In the early acute period, articular involvement is generally transient and usually clears without leaving residual damage Chronic granulomatous coccidioidal arthritis is often mistaken for tuberculous arthritis This condition is serious, progressive, and destructive of bone and cartilage Diagnosis is dependent on demonstration of the causative organism in tissues from the areas which are involved

Specific therapy has not been devised for chronic coccidioidal infection, and as the process tends to metastasize, early recognition should call for careful consideration of amputations as possible lifesaving measures

Histoplasmosis This condition is a chronic generalized disease caused by infection with *Histoplasma capsulatum* Its usual manifestation is in the form of a chronic, wasting febrile illness with enlargement of the liver and spleen, anemia, and leukopenia Pulmonary lesions, widespread skin eruptions and diffuse lymphadenopathy are frequent complications Involvement of a knee joint has been reported in one individual Amputation was performed in this instance No other effective therapy has been devised for histoplasmosis

Meningococcal Arthritis Articular complications associated with meningococcal infections may be one of three varieties (1) arthralgias occurring during the first few days of the infection and often appearing simultaneously with cutaneous hemorrhages articular involvement of this period is transient resolving without suppuration (2) suppurative meningococcal arthritis involving usually a single joint (often a knee), this condition is associated generally with effusions of serous or seropurulent fluid (3) arthralgias of serum sickness, this has rarely

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acterial infection of the joints

Actual invasion of joints by Brucella is are, occurring perhaps in only 1 or 2 per ent of cases In such cases there may be netastatic infection associated with brucellar epticemia or extension may occur to joints rom adjoining foci of brucellar osteomyelitis Almost any joint may be affected in the lat er types of cases but spinal joints have been he most frequent sites of such involvement

A true estimate of the value of various herapies for brucellosis is difficult because of varying courses exhibited by the disease in different individuals Not infrequently pa ients recover spontaneously although ap parent recovery may be followed by recrudescences

Treatment of articular complications of brucellosis is essentially the problem of treating the underlying disease For this purpose combined sulfadiazine and streptomycin therapy has been most successful If suppuration ensues, incision and drainage may be required

Remarkable recoveries from brucellar ar thritis following oral administration of aureo mycin have been reported recently Doses employed were 0 1 gm the first day, 0 6 gm the second day, 1 6 gm the third day, and 2 gm the fourth day Thereafter the daily dose was increased to 4 or 6 gm The latter amounts were administered for 2 to 14 days

If chloromycetin is used, the initial dose should be 2 to 3 gm followed by 0 25 gm every 3 hours until the temperature has been normal for 5 days The effect of terramycin remains to be studied

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INTERMITTENT HYDRARTHROSIS

This curious remitting disease of joints was first described in modern medical literature in 1831 By 1939 the number of reported cases was only 106 Thus, in more than 100 years the incidence of reported cases was approximately one each year This impression of great rarity is not justified, as, without doubt, many cases have been observed but not reported Certainly intermittent hydrarthrosis is not infrequently encountered among clients of arthritis clinics and rheumatism spas

The distinctive symptom of this condition is regularly recurring articular swellings, lasting but 4 days to a week Periods of freedom range from a few days to a month Occasionally several joints are affected

Two varieties are encountered The first has been designated "symptomatic intermittent hydrarthrosis because the swellings are believed to be early symptoms of rheumatoid arthritis In this form attacks recur regularly for varying periods but remissions tend to disappear as attacks gradually merge into persisting articular inflammation Sometimes one or more joints other than those taking part in the recurring swelling display evidences of chronic arthritis

A second form has been called "idiopathic" because it is believed not to be a forerunner of rheumatoid arthritis

Speculations and research concerning the etiology of intermittent hydrarthrosis have not thus far led to a satisfactory conclusion The periodicity of attacks suggests an allergic reaction either to bacteria or to some other irritants However, evidence which has thus far been brought forward in support of allergy as a cause has not been impressive Patients with intermittent hydrarthrosis do not regularly suffer with other allergic symptoms such as angioneurotic edema, hives,

asthma or hay fever and usually do not respond to antiallergic measures

A case has been reported in which organisms of the brucella group were found in synovial fluid removed during an episode However search for these and other organisms in patients studied by this writer has been unsuccessful

An endocrine dysfunction is suggested by several patients who experienced remissions during pregnancy also because of the analogous cyclic character of menstruation

Treatment Results of most treatments have been disappointing Rest in bed administration of salicylates aspiration of fluid and administration of streptococcal vaccines have regularly failed to bring the process to a halt Attacks may disappear spontaneously while a patient is under observation a consideration which makes for great difficulties in interpreting the value of any treatment measure

During acute attacks patients are more comfortable at rest but if it is necessary for the patient to continue activity during attacks the swollen knee should be supported

Other treatment measures worthy of trial include intravenous administration of typhoid vaccine as described under rheumatoid arthritis removal of obviously infected foci and avoidance of foods to which the patient is definitely sensitive

In 2 instances reported by Krida a cure followed synovectomy but this operation has not prevented the appearance of a progressive arthritis (sometimes in other joints) following synovectomies performed on patients observed by this writer

Roentgen therapy halted recurrences in one patient as recorded recently by Ragan This patient received eight treatments each of 225 r at 25 cm distance 2 ma intensity

also reported the case of a patient whose attacks ceased following treatment with gold sodium thiomalate Both measures seem worthy of trial if simpler measures fail.

Desensitization to histamine by means of intravenous and intramuscular injections has repeatedly failed to influence the course of the disease in my patients I no longer attempt this procedure

Attacks have ceased following administration of ergotamine tartrate in doses of 1 mg daily given for approximately 2 months followed later by repeated courses of 1 tablet daily for periods of about a month when attacks tended to recur

The prognosis is uncertain In some cases regular recurrences of attacks continue for years even for two or more decades without change in symptoms In many instances the patient eventually displays a full blown" picture of rheumatoid arthritis

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GOUT

Gout is a metabolic disease the outstanding features of which are recurring episodes of articular inflammation later becoming chronic tophi (deposits of urate crystals in articular periarticular or subcutaneous tissues cartilages and kidneys) and a notable tendency toward hyperuricemia

Symptoms of gout generally progress in an orderly and developing pattern knowledge of which is essential for prompt recognition and proper treatment For this reason special attention is given to certain general considerations before discussing treatment The specific metabolic anomaly which lies at the basis of gout may be inherited in some and possibly in all patients with this disorder Between the moment of acquisition and appearance of the articular phenomena a period elapses which may be designated as a larval period During this time the patient may have no symptoms or occasionally may

Advent of articular attacks may be considered as marking the opening of the second

period of gout During this second period patients characteristically suffer repeated attacks of acute, self limited arthritis Such attacks may appear without premonition, have a predilection for the feet and especially for metatarsophalangeal joints of the great toe, but not infrequently affect other joints of extremities Early attacks generally but not always remain monarticular Accompanying pain is variable, being moderate in some but violent in others Such attacks last several days or at most a week or two and recur at intervals of months or years Hyperuricemia is more frequently encountered during the

tered with increasing frequency after onset of articular attacks and a notable tendency is observed for gouty individuals to experience episodes of olecranon bursitis and renal colics from passage of uratic gravel

After numerous and prolonged articular at

serious crippling results from extensive damage to joints in this period

Chronic nephritis, recurring renal colics and extensive deposits of tophaceous material in periarticular and subcutaneous tissues are characteristic complications of the third period Tophi may assume huge proportions and destroy the overlying integument, producing sinuses through which crystalline urates and other necrotic material

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of a disturbed chemical mechanism for the handling and disposition of uric acid This fact has been evident for more than a century and a half since Wollaston demonstrated urates in tophaceous material in 1779 The seat of this anomalous disorder has not yet been found, although recently important new facts have come to light concerning patho

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ketosteroid compounds at a lower rate than nongouty individuals In addition balance studies of electrolyte and water metabolism have disclosed evidence suggesting that acute attacks tend to occur at times of decreased adrenal cortical activity Also acute gouty arthritis has been terminated abruptly by administration of adrenocorticotropic hormone (ACTH) but attacks have often reappeared within a few days after withdrawal of this hormone

These observations suggest that the adrenal cortex plays an important role in

necessary to await further study of these phenomena to apply these observations to treatment

Treatment Reasonably effective therapeutic measures have been evolved for the several phases of gout These can be expected to produce prompt and complete relief in most instances But, success in treatment is dependent upon the establishment of a correct diagnosis, on an accurate estimate of the condition of the patient, and on the wholehearted co operation of the patient himself

Treatment During the Larval Phase of Gout Identification of the disease during this period is most often accomplished in family members of affected patients When the diagnosis is made, it is reasonable to recommend that the patient eat in moderation of foods containing purines, avoid alcohol choose occupations which do not entail exposure to lead and which do not encourage excesses in eating An incident of articular pain should call for a careful review of the situation and if it is determined that the larval period has progressed into the second period of acute articular attacks, a more in

ring Acute Gouty Arthritis Treatment of a patient in this phase of gout requires two sets of instructions These should include instructions for periods between attacks and instructions for treatment of acute attacks

Attack free Intervals After a patient has recovered from an acute attack he enters a period when he is in danger of the next attack. The aim of treatment for this period should be to minimize progressive tendencies of the defective urate metabolism thereby reducing incidence of further attacks

Diet To reduce the metabolic load, purine containing foods should be allowed only in moderation Protein foods, low in purine content, including particularly milk, cheese, eggs and breads, should be substituted for meat Bulk, vitamins, and mineral requirements are provided by vegetables and fruits Caloric needs should be taken into account in planning this diet Several sample menus are illustrated in the charts On this regimen meats are permitted in carefully limited amounts and glandular meats such as sweetbreads, liver and kidneys are excluded entirely Certain vegetables and cereals which contain notable amounts of purines are permitted only sparingly

During attack-free intervals it is best to allow no foods containing significant amounts of purines—in other words, a purine free diet—during 2 or 3 days of each week For the remaining days the diet is planned to be low in, but not free of purines For the patient with gout of average severity a small serving of nonglandular meat can be allowed on 3 days of each week Other purine containing foods should be omitted on these days One serving of vegetable such as lima beans, spinach mushrooms, or a serving of whole grain cereals such as cooked whole wheat, wheat biscuits, or oatmeal, may be allowed on 2 additional days

Foods permitted on this diet include refined cereals such as cream of wheat, cornflakes, and puffed rice White or fine rye bread is used in place of whole wheat bread Butter, cream, mayonnaise, and other fats are permitted only in moderation because of the observation that uric acid in plasma tends toward higher levels in patients who are permitted a high fat intake

For desserts, fruits are satisfactory but if the patient is not overweight he may occasionally have icecream, tapioca, or cornstarch pudding sherbets, and ices Desserts to be avoided include those rich in fats such as chocolate cake or pudding, spiced cake or cookies, pies, and homemade icecream

Coffee tea, cocoa coca cola, and "pop" do not give rise to important quantities of uric acid and may be included in the diet if proper allowance is made for content of calories

Medications In addition to dietary restrictions, regular weekly courses of salicylates, 75 to 90 grains (5 or 6 gm) on 3 to 5 consecutive days of each week aid in effecting excretion of urates and maintenance of lower levels of urate in serum To prevent crystallization of urates in urine during periods of urate diuresis associated with administration of salicylates in this manner, sufficient baking soda should be given to alkalinize the urine The specific dose to be used is determined by testing the urine with litmus paper

To some extent at least a physician may test the degree of control which he has achieved by occasional determinations of

abnormal break down of cells, a rising level of serum urate often denotes poor co operation on the part of the patient

Treatment of Acute Attacks Rest for Affected Joints When an attack appears the extremity should be placed at rest Generally it is necessary for the patient to go to bed The foot or arm should be elevated on pillows to minimize a tendency to swell For all but the mildest attacks, complete rest must be continued until the attack is well controlled Premature return to activity is not infrequently followed by recrudescence of attacks Patients should be urged not to attempt to "walk it off"

Applications of Heat Properly prepared hot wet compresses are effective in alleviating pain Prior to applying wet cloths, the skin should be smeared with vaseline or cold cream to prevent excessive maceration Compresses should be generous in size, large enough to cover the affected joint and an extensive area beyond the site of the attack A thin blanket may be wrapped about the wet compresses to reduce the speed of cooling Compresses should be changed at intervals of 1 or 2 hours and their application should be continued until the attack is well under control When possible, wet packs should be constantly applied for the duration of an attack through the day and night

Colchicine At the first sign of an attack a patient should start a course of colchicine This ancient remedy is now available in a potent form, as tablets or pills each of 1/100 or 1/120 grain (0 65 or 0 53 mg) A course may be defined as the number of tablets

which suffices to relieve an attack or produce diarrhea Ordinarily one may give the patient 2 tablets to start then one every hour until a loose stool results Patients require on the average from six to fifteen doses before diarrhea appears

Patients with gout should have colchicine readily available and should be instructed to take the tablets immediately upon appearance of symptoms which suggest that an attack is starting

The mechanism of colchicine s action *remains obscure When administered in* amounts sufficient to produce gastro intestinal irritation no shift in level of blood uric acid can be detected nor is there any increase in rate of excretion of uric acid The drug is nonetheless effective in spite of this failure to influence the metabolism of uric acid One writer stated recently that "over 95 per cent of acute attacks are materially benefited by a single course" Occasional instances are encountered in which the drug fails to produce such sharp remissions and for these attacks a second or even a third course may be employed

Diet During attacks the diet should be purine free that is free of foods containing abundant cell nuclei This diet should also be low in fat which favors retention of urates *Milk cheese eggs cereals vegetables and* fruits constitute the chief categories of foods for this period Vegetables which contain moderate amounts of purines should be avoided during acute attacks These include particularly beans peas lentils and spinach Coffee tea and chocolate which do not give rise to uric acid need not be eliminated from the diet

Other Medications Both cinchophen and sodium salicylate cause notable lowering of serum urate levels and an increased rate of *excretion of uric acid in the urine For acute* attacks sodium salicylate may be given in doses of 75 to 120 grains (5 to 8 gm) daily for the duration of the attack In particularly severe instances when attacks persist in spite of other measures the writer uses cinchophen in doses of 0 5 gm three times daily I know of no instance in which cinchophen hepatitis has been encountered in a gouty patient

Narcotics Pain of gouty arthritis is occasionally intense and may necessitate administration of codeine 30 mg morphine 15 mg or other narcotics

A Note Regarding Certain Provocatives of Gouty Arthritis A wide variety of physical occupational pharmacologic and psychologic stimuli have been observed to provoke attacks of acute gouty arthritis in susceptible persons These have been studied in detail

kept in mind by physicians responsible for *management of patients with gout and avoid*ance of known provocatives must be considered an important therapeutic measure

Among physical traumata to be avoided whenever possible are the following (1)

radic participation in sports or hobbies (5) certain drugs including bile salts concentrated solutions of thiamine chloride liver extracts (except when their use is absolutely essential for treatment of pernicious anemia) and mercurial diuretics Patients with both diabetes mellitus requiring insulin and gout should take special care to avoid insulin reactions as these occasionally provoke acute *attacks Strong purgatives which are capable* of altering fluid balance even temporarily should be avoided for the same reason

Surgical procedures of all types may be followed by exacerbations of gouty arthritis in susceptible patients Incidence of such

doses of 75 to 90 grains (5 or 6 gm) On the *day of operation and for a week or 10 days* thereafter resume the same program If the drug cannot be taken by mouth similar amounts should be given intravenously

The Adrenocorticotropic Hormone in Gout Repeated observations have shown that acute attacks of gout can be quickly overcome by administration of small amounts of this hormone Patients so treated at the Michael Reese Hospital responded within a few hours after administration of 25 to 50 mg of potent material A problem which remains to be

solved concerns a tendency for attacks to recur within a few days after withdrawal of this hormone A practical application cannot as yet be predicted

Treatment of the Third Phase of Gout—The Phase of Chronic Gouty Arthritis Chronic articular deformities, large subcutaneous tophaceous deposits renal and vascular complications of the disease constitute the main problems for treatment in this period For chronic articular deformities physical therapy procedures are occasionally of value Applications of heat from infra red bakers, warm moist compresses for flare ups of articular inflammation, and mild stimulating massage for wasted muscles are worthy of use When tophaceous material causes deformities which interfere with the use of extremities, an orthopedic surgeon can, at times, greatly improve the situation by tophectomies combined with plastic restoration of damaged regions

For cardiovascular and renal complications of chronic gout no specific measures are available However, to the therapeutic program indicated by the particular complication should be added strict dietary precautions, together with use of purine diuretics as described above

Some consider continuous administration

diuretic powers and may be used to supplement either salicylates or cinchophen in severe cases

POINTS TO REMEMBER ABOUT A PURINE FREE DIET

(1) *Always avoid*

Alcohol	*Meats*	*Onions*
Anchovies	Fish	Peas
Brains	Fowl	Spinach
Gravy	Asparagus	Whole-grain cereals
Kidneys	Cauliflower	Malted cereals
Liver	Kidney beans	Whole grain bread
Meat extracts (juices)	Navy beans	
Sardines	Lima beans	
Sweetbreads	Mushrooms	

(2) *Use in Moderation*

Condiments — All fats — Rich desserts

(Uric acid is more readily excreted when the fat in the diet is moderately restricted)

(3) *Use two eggs or egg substitute per day*

Substitutes for one egg:
- 2 tablespoons cottage cheese
- 1 inch cube cheese
- 1 cup custard
- 1 glass milk

(4) Choose abundantly the foods that are purine free consistent with the maintenance of normal weight

POINTS TO REMEMBER ABOUT A LOW PURINE DIET

th the
, 2 oz
meat

is omitted on those days

SAMPLE MENU—PURINE FREE AND LOW PURINE—1250 CALORIES

Purine Free Diet

This gives an idea of the amount and kind of food permitted when WEIGHT REDUCTION FEATURES NEED TO BE INCLUDED IN THE DIET INSTRUCTIONS

Breakfast	Fruit fresh	1 serving
	Egg not fried	1
	Bread white (may be toasted)	1 slice
	Butter	½ square
	Beverage tea or coffee, as desired	
10 00 A M	1 glass unsweetened fruit juice with 1 beaten egg white	

Dinner	Eggs	2 or egg substitute
	Vegetable no purine	1 serving
	Salad (permitted foods)	1 serving
	Bread white	½ slice
	Dessert fresh or unsweetened fruit	1 serving
	Milk skimmed	1 glass
	Beverage tea or coffee as desired	
	3 00 P M 1 glass unsweetened fruit juice with 1 beaten egg	
Supper	Eggs	2 or egg substitute
	Vegetable no purine	1 serving
	Salad (permitted foods)	1 serving
	Bread white	½ slice
	Butter	½ square
	Dessert fresh or unsweetened fruit	1 serving
	Milk skimmed	1 glass
	Beverage tea or coffee as desired	
	8 00 P M or before retiring 1 glass of unsweetened fruit juice with 1 beaten egg white	

For adequate vitamin C include one serving of citrus fruit or tomato in some form each day Vitamin supplement as directed

Note For the low p[illegible] plemental all[illegible] product) for c[illegible] be omitted fo[illegible] for that day a purine containing vegetable may replace a non purine vegetable or a whole grain bread or cereal may replace white bread or refined cereals for the meal

SAMPLE MENU—PURINE FREE AND LOW PURINE—2500 CALORIES

Purine Free Diet

This menu shows the amount and kind of foods permitted for persons engaged in moderately active work or for less active persons who need to gain weight

Breakfast	Fruit	1 serving
	Cereal no whole grain	1 serving
	Egg not fried	1 or egg substitute
	Bread white may be toasted	1 slice
	Butter	1 square
	Cream coffee	2 tablespoons
	Milk for cereal	½ glass
	Beverage tea or coffee as desired	
	Jelly or preserves	1 tablespoon
	Sugar	
	10 00 A M 1 glass sweetened fruit juice	
Dinner	Soup if made from allowed milk and vegetable	1 serving
	Eggs	2 or egg substitute
	Potato or substitutes not fried	1 serving
	Vegetable no purine	1 serving
	Salad (permitted foods)	1 serving
	Bread white	2 slices
	Butter	1 square
	Dessert fruit or simple dessert	1 serving
	Milk	1 glass
	Beverage tea or coffee as desired	
	Jelly or preserves	
	3 00 P M 1 glass sweetened fruit juice	



SAMPLE MENU—PURINE FREE AND LOW PURINE—2500 CALORIES—(*Continued*)

Supper	Eggs	2 or egg substitute
	Potato or substitute not fried	1 serving
	Vegetable no purine	1 serving
	Salad (permitted foods)	1 serving
	Bread white	2 slices
	Butter	1 square
	Dessert fruit	1 serving
	Milk	1 glass
	Beverage tea or coffee as desired	
	Jelly or preserves	1 tablespoon
	8 00 P M or before retiring—1 glass sweetened fruit juice	

For adequate vitamin C include 1 serving of citrus fruit or tomato in some form each day
Vitamin Supplement as directed

Note For the low purine diet the same general suggestions should be followed with the

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FIBROSITIS

Among patients of rheumatism clinics and arthritis centers a large proportion complains of a distinctive group of symptoms involving muscular and articular aching and stiffness, yet these patients do not show evidence of inflammatory or degenerative damage to joints or muscles The term fibrositis has been assigned to this syndrome for want of a better designation

In terms of this concept, fibrositis is defined as a clinical syndrome (not a pathologic entity) acute subacute or chronic, apparently involving subcutaneous tissues, fibrous origins insertions and aponeuroses of muscles, articular capsules, ligaments, tendons and possibly encapsulating membranes of nerves Characteristic symptoms are pain and stiffness aggravated by inactivity, partially relieved by exercise, use, applications of heat, massage or simple analgesic drugs such as aspirin These symptoms are often aggravated in anticipation of changing weather, and are made worse by excessive use, profound psychic disturbances and by systemic infections such as colds or influenza

Aside from an important necessity to distinguish fibrositis from chronic arthritis it is also important to separate this condition from the commonly occurring form of psychoneurosis which manifests itself especially in complaints of pain in muscles and joints The latter distinction is usually de

especially difficult when patients with fibrositis show evidences of psychoneurosis also As in all diseases, the physician must often deal both with organic and psychic disturbances in the same individual

Fibrositis may be classified not only in terms of its acuteness but also according to location Thus, a physician may expect to encounter certain distribution patterns in patients with this disease Symptoms may be mainly intramuscular, as in wryneck or lumbago Symptoms may be largely confined to regions about joints as about the small joints of the hands, about the knees or about a shoulder Tendons and fasciae are predominant sites of involvement in some cases, as for example in Dupuytren's contracture of palmar fasciae in tennis elbow, and in plantar fascitis Rarely, sheaths of nerves are seemingly involved with resulting neuritis like symptoms

Superimposed on various other ailments including *rheumatoid arthritis* rheumatic fever, gouty arthritis, and many generalized

fections some patients have symptoms in distinguishable from those of primary fibrositis For this situation the term secondary fibrositis seems justifiable A treatment for these secondary forms of fibrositis is usually a matter of proper treatment for the underlying disease In the discussion on treatment which follows only primary fibrositis will be considered

Treatment Having established a diagnosis of primary fibrositis the physician must usually take time to explain the nature of this ailment to the patient In this condition as in osteo arthritis many patients suspect the worst assuming they are afflicted with a deforming disease Often assurance is the only measure of treatment needed and when properly assured many patients tolerate fibrositis philosophically without systematic therapy

Definitive therapy of fibrositis has not been evolved The etiology of this condition remains unknown and developing knowledge of hormone therapy for rheumatoid arthritis has not yet progressed to a point where relationship to fibrositic conditions can be discerned Under present circumstances therefore treatment remains empiric but reasonably satisfactory measures have been evolved through years of patient clinical observation

Useful measures include regulation of rest physical therapy analgesics removal of infected foci and for some patients foreign protein therapy

Employment of rest should be patterned to the intensity of symptoms For violent acute episodes as in acute torticollis lumbago or acutely painful shoulder affected parts should temporarily be placed at complete rest For chronic intramuscular fibrositis accompanying fatigue generally dictates regular periods of midday rest combined with extra hours of rest in bed at night

Physical therapy procedures worthy of use are preferably simple measures capable of employment in the home These include warm baths electric pads simple electrical bakers or infra red bulbs Local heating is often especially comforting if followed by a few minutes of firm massage

Occasionally patients derive additional comfort from physical therapy administered by trained technicians For usual cases home measures suffice if supplemented by professional treatments once or twice weekly

Focal Infection Comments on focal infection in relation to rheumatoid arthritis may be applied to fibrositis In general it seems reasonable to suggest removal only of obviously infected foci

Aspirin or sodium salicylate are the most efficient of the analgesic drugs These are administered in dosage of 10 grains (0 6 gm) every 3 to 4 hours as necessary for pain or discomfort Patients need to be assured that continued occasional use of salicylates is without harmful effect Rarely violent episodes of shoulder pain or lumbago require codeine or other narcotics

Employment of local anesthetic injections into "trigger zones" is popular in some clinics Five or 10 cc of 1 per cent procaine solution may be injected into painful regions without harmful effect For some patients this procedure seems to provide a degree of relief although the relief is rarely maintained This procedure has been employed particularly in treatment of acute episodes as for example in patients with acutely painful shoulder

Roentgen therapy vitamins particular dietary factors curare like drugs and various hormones have been employed but proof of their effectiveness is lacking and none are recommended

Symptoms of fibrositis have been relieved during pregnancy and during episodes of jaundice It is to be hoped therefore th development of knowledge concerning st roids and other forms of hormone thera may prove their value in the treatment fibrositis

Edward F Rosenber

OSTEITIS DEFORMANS
(Paget's Disease of the Bone)

Although James Paget first described bone disease that bears his name in we still have no clear concept of its ca is a form of fibrous dysplasia of bone a localized disease and is never gener it may involve one bone (monostotic or many (polyostotic form) The m quently involved bones are the sacrum femur cranium sternum pelvis tibia ribs and humerus in that o

occurs almost exclusively after 40 years of age, but has been described in patients as young as 21 years

At present there is no effective treatment of the essential lesion of this disease, so that we are reduced to treating its complications

Pain Probably in the majority of patients with Paget's disease the condition is entirely asymptomatic and the diagnosis is made in the process of roentgen examination of the bones for other causes However, in other patients "bone pain" may be the presenting and very troublesome complaint At times pain in an extremity may be due to inadequate circulation because of associated arteriosclerosis This association of arteriosclerosis and Paget's disease of the bone is so common that some writers have assumed an etiologic factor to be present

Gill and Stein recommend the use of calcium carbonate by mouth 4 gm of the powder being given two or three times daily, unless the stools become loose in which case the amount is decreased A diet low in calcium is also recommended Newman in reporting a statistical study of 82 cases, states that 6 of 8 patients so treated show symptomatic improvement within 1 to 2 months while on this therapeutic regime, but symptoms promptly recur when they are taken off it

Roentgen therapy has been used on an empiric basis for relief of pain and does seem to be of some value A few hundred roentgen units are given over the painful area as in the treatment of chronic inflammation with this means There is no proof that roentgen therapy causes malignant degeneration in the involved bone Osteogenic sarcoma was formerly believed to occur in 7 per cent of cases This figure is now held to be much too high

Fractures Fractures of weight bearing bones are prone to occur owing to the weakened condition and are almost always transverse fractures Not infrequently a "fatigue fracture develops This appears on the roentgenogram as a transverse radiolucent zone at the site of greatest strain (usually the area of the apex of the bow in the bent long bone) on the convex side At first the fracture is incomplete and resembles the "march fracture, or the fracture seen in marked osteomalacia described by Milkman, it may go on to completion, usually, however, without great displacement of the parts These fractures as a rule heal readily in the usual length of time and with abundant callus Special emphasis should be placed on keeping the patient ambulatory if at all possible When a fracture occurs in a bone involved in Paget's disease, a stimulus for bone production by the stress and strain of normal use is removed, but the destructive process continues unabated This may lead to a hypercalcemia and a hypercalciuria if the amount of calcium to be excreted exceeds the ability of the kidneys to excrete it or if the kidney function becomes impaired from hypercalciuria If it becomes necessary to immobilize the patient with fracture complicated Paget's disease the blood calcium level should be watched, fluids forced and a diet low in calcium given

Cranial Nerve Injury Loss of hearing [illegible]

ear in the disease process, rather than to a compression of the auditory nerve, Roentgen therapy may relieve the tinnitus and dizziness

Kyphosis The bodies of the spine are frequently involved and a gradual deformity develops as a result of wedging compression of the softened bone This process of wedging occurs so gradually, like the bowing of long bones that no fracture can be said to occur, and the process is not particularly painful

Stasis Ulcers When Paget's disease involves the tibia, it may become so enlarged that the circulation, especially the venous return of blood, is interfered with, and stasis ulcers develop These are best handled by the application of Unna's paste boot A section of the boot, approximately two or three times the diameter of the ulcer, is then removed to permit the application of wet dressings to the ulcer We prefer to use several flats soaked with a tyrothricin solution and applied under moderate pressure from an elastic bandage as the wetting and antiseptic agent The dressing should be changed infrequently

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OSTEOPOROSIS

Osteoporosis is a condition in which there is reduction of the bone mass in the body it is characterized by a lack of osteoblastic activity

Osteoporosis occurs in the following clinical conditions

(1) Disuse atrophy

(2) Senile osteoporosis usually a result of several factors physical activity decreases with age so that the need for bone is less a state of chronic malnutrition may occur where the protein requirements of metabolism are not fulfilled in addition the anabolic processes in the body generally are diminished in old age and bone tissue like other tissues (hair skin muscle etc) atrophy

(3) Malnutrition There are insufficient protein building blocks which the osteoblasts may convert into osteoids In osteoporosis the fault is with tissue metabolism as distinguished from calcium metabolism

(4) Cushings Syndrome It is believed that in this condition there is an excess of adrenal cortical "sugar" hormones which inhibit the metabolism of protoplasm in general including the anabolism of osteoid

It has been postulated that the adrenal cortex produces a "sugar hormone" and a "nitrogen hormone" that the S hormone is antianabolic and that the N hormone is like testosterone and neutralizes the S hormone that in Cushings syndrome there is an excess of S hormone Clinically it was found that testosterone propionate in a dosage of 25 mg daily had a markedly beneficial effect on the nitrogen phosphorus and calcium balance of these patients

(5) Postmenopausal osteoporosis is the commonest of all forms of osteoporosis and is due to the deficiency in estrogen production with attendant lack of stimulation of osteoblastic activity The osteoporosis involves chiefly the spine and to a lesser degree the pelvis and skull It usually does not occur before the middle 50's but where artificial menopause has been produced it may occur at a much earlier age

Albright recommends the use of both estrogen and androgen in the treatment of senile and postmenopausal osteoporosis and gives the following dosage

Estrogens Diethyl stilbesterol 0 5 to 1 [illegible] muscularly estradiol dipropionate 5 mg weekly intramuscularly

Androgens Methyltestosterone 10 to 20 [illegible]

[illegible] should be interrupted for 1 to 2 weeks each 4 to 6 weeks since estrogenic therapy may lead to development of cancer if the uterus [illegible] be investigated further

There are numerous drawbacks to the administration of sex hormones in the treatment of senile osteoporosis and the writer is not entirely convinced of their necessity Hormonal treatment is expensive for the patient The treatment must be continued over long periods of time and even then it has been difficult to produce undisputed roentgenographic evidence that the bones have become more calcified than before the therapy was instituted Testosterone compounds must be handled with care because of the masculinizing effect Most women will not tolerate more than 300 mg of androgen a month Steroid therapy may cause sodium retention and an elderly patient may develop edema especially if the serum pro-

tein level is low It may be necessary to use a low salt diet and to give ammonion chloride The writer has reported his experiences in the treatment of a large series of compression fractures of the spine many of which occurred in elderly people with senile osteoporosis Most of these patients were treated without estrogen therapy and made good functional recovery

Orthopedic Management It is important that long periods of immobilization or bed rest be avoided in these patients otherwise disuse atrophy of bone is accentuated Many persons with senile osteoporosis with or without the complication of compression fracture may be treated as ambulatory patients The back may be strapped with adhesive tape for 2 or 3 weeks followed by the wearing of a simple well boned corset Several brief rest periods on a firm flat bed and physiotherapy consisting of active exercise and postural training are given If spinal fracture is superimposed on the osteoporosis hospitalization for 10 to 20 days is usually necessary Muscle spasm is relieved by hot compresses and by uninterrupted rest or possibly by traction (bilateral Russell) Frequent passive change of position ("all in one piece") is insisted on as well as active use of the arms and legs even in the acutely painful stage Within a few days the pain on movement disappears the patient is started on gentle active postural exercises fitted with a high front laced corset and resumes normal activities

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OSTEOMALACIA

Osteomalacia is a disorder of the skeleton in which bone matrix or osteoid is not promptly and properly calcified In this condition there is nothing wrong with the process of the manufacture of osteoid the fault lies in its calcification and in this it differs in its pathologic physiology from osteoporosis and from osteitis fibrosis due to hyperparathyroidism which are characterized respectively by poor production of bone and by too rapid destruction of bone

Osteoid is produced by action of the osteoblasts and these are stimulated to activity chiefly by the stress and strain of use The calcium ions are absorbed from the acid chyle of the upper intestinal tract and deposited where needed in the skeleton probably largely through the action of the enzyme alkaline phosphatase The action of vitamin D is twofold (1) to aid in the absorption of the calcium ion through the gut wall (2) to increase the excretion of phosphorus into the urine This second action is the same as the action of the parathyroid hormone and is of importance only when excessive dosage of vitamin D is present

Osteomalacia may be due to one or more of the following causes

- (1) Insufficient intake of calcium
- (2) Adequate intake but inadequate absorption
  - (a) simple lack of vitamin D
  - (b) resistance to vitamin D
  - (c) steatorrhea
  - (d) achlorhydria
- (3) Adequate absorption but inadequate deposition into the matrix
  - (a) renal acidosis
  - (b) idiopathic hypercalciuria

The Food and Nutrition Board of the National Research Council recommends 0 8 gm of calcium per day for an adult man or woman A half pint of milk (240 cc) furnishes 0 27 gm of calcium most of which is available for absorption A half pint of plain icecream furnishes slightly less calcium A half ounce of cheese furnishes 0 25 gm of calcium Green and leafy vegetables

cium intake is from 1 5 to 2 gm per day Children require from 1 to 1 5 gm

Osteomalacia due to simple lack of vitamin D is probably rarely seen in the United States Osteomalacia in children (rickets) in its mildest form at least is quite common

This condition will respond to the usual small doses of vitamin D

Some individuals apparently develop a resistance to vitamin D, so that the minimum daily requirement for adequate calcium absorption (400 international units) may be totally inadequate and tremendous doses of 100 000 to 300 000 units a day may be necessary to achieve the desired results

Steatorrhea is present in children with celiac disease and in adults with chronic pancreatitis sprue and in the insufficiency of the small intestine following certain short circuiting operations on the bowel If there is a fecal fat content of 10 per cent of the fat intake steatorrhea is said to be present Steatorrhea results in an osteomalacia inasmuch as the fat soluble vitamins including vitamin D, are dissolved in the fat and passed through the intestine unabsorbed A low fat diet should be prescribed with vitamins given between meals so that they will not dissolve in the intestinal tract or an injectable form of vitamin D may be given It must be remembered that all the fat soluble vitamins must be provided (D K A and E as alpha tocopherol) for in steatorrhea both the vitamin K and the vitamin A levels may be low with increased bleeding time as well as a low serum carotinoid

Theoretically, an achlorhydria will also result in inadequate absorption of calcium since the calcium salts are soluble in acid media but insoluble in alkaline media However at this time we have no certain knowledge that the administration of hydrochloric acid in the achlorhydric animal is of value in the treatment of osteomalacia

When osteomalacia is associated with renal acidosis resulting from tubular insufficiency without glomerular insufficiency calcium appears in the urine in increased amounts This causes the serum calcium to fall which in turn results in parathyroid hyperplasia increase in excretion of phosphorus and a hypophosphatemia A demineralization of bone in this instance is treated

tion of alkali to decrease the loss of calcium in the urine Fuller Albright et al recommend a solution of 140 gm of citric acid and 98 gm of sodium citrate in 1000 cc of water The patient takes from 50 to 100 cc of this mixture daily, depending on the amount needed to overcome acidosis The citric acid helps to acidify the gastric content but is burned after absorption

Renal rickets is not the same condition as renal acidosis due to tubular insufficiency In renal rickets there is an associated glomerular insufficiency, and the acidosis is due not only to the excretion of the base but also to the retention of the acid radicals and is not immediately corrected by giving base Renal rickets is not an osteomalacia but rather an osteitis fibrosis cystica generalisata since the emphasis is on bone destruction rather than on lack of calcification of new osteoid

VERNON C TURNER

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MYASTHENIA GRAVIS

In general the recognition of myasthenia gravis is not difficult if one keeps in mind that the first manifestations are usually the characteristic fatigability following minor exertion and the muscular weakness increasing with effort and diminishing with rest and that these are sometimes only to be seen in the external ocular muscles and

General muscular weakness of the extremities neck and trunk commonly show up only in the later stages, and only exceptionally does one see a patient in whom a particularly exhausting muscular effort has precipitated a myasthenic reaction as the first evidence of the disease Such a manifestation was once noted by the writer in the leg muscles of a young girl after her first

tiring bicycle excursion The history of most patients shows that abnormal muscular fatigue occurs before loss of power Once the disease is established, muscles with normal power at the beginning of effort become incapable of sustained contraction with continued effort In the early stages or in the mild form of the disease, the more or less normal mu co lar tr ngth f ll

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visible features of the functional paralysis, the variability of the muscular strength is characteristic, as is also the unpredictability of its course In untreated patients under 25 years of age, the prognosis is regarded as most serious, and formerly these young people died in 1 or 2 years On the other hand, young patients in early stages of the disease may have the best and longest spontaneous remissions, such remissions having been observed up to 20 years or more

Doubtful cases of myasthenia gravis may be recognized by employing the therapeutically effective prostigmine (neostigmine) as a diagnostic test Viets and Schwab's combined mixture of 1 5 mg of neostigmine methylsulfate with 0 6 mg of atropine sulfate in a single ampule given intramuscularly is now generally used for this purpose, but we have found the intravenous administration of 0 5 mg of neostigmine methyl sulfate preferable The nature of the disease is still obscure A deficit of acetylcholine at the nerve terminals or a decreased acetyl choline synthesis (Torda and Wolff), increased destruction of acetylcholine by a surplus of cholesterinase, the continuous presence at the motor end plates of a paralyzing agent of curare like nature, or its gradual accumulation during muscle action leading to a raised threshold of muscle fiber excitability, a disturbance of potassium metabolism, are all possible etiologic factors (A Schweitzer)

Drug Therapy In spite of the great progress made since Mary Walker (1935) first showed the dramatic effect of prostigmine on myasthenic musculature, the treatment of myasthenia gravis is still symptomatic, and no cure is known In fact, the very mode of action of prostigmine is still debated and the possibility of its acting directly on myasthenic muscles by a hitherto unknown mechanism will have to be seriously considered Thus the basis for the use of prostigmine as an antidote of curare, the poisoning effect of which resembles the myasthenic state, is possibly less solid than was generally thought

However, prostigmine (neostigmine) is the drug of choice to combat the muscular weakness in myasthenia It is used most often as prostigmine bromide in 15 mg tablets for oral administration, and as prostigmine methylsulfate in 0 5 mg ampules for intramuscular injection Every patient presents his own therapeutic problem and the success or failure of the treatment depends greatly on the optimal co operation of patient and physician Lack of intelligent understanding on the part of the patient as to the purpose and limitations of the treatment is as detrimental to therapeutic success as failure on the part of the physician to determine the proper type and dosage The patient should be informed of the substitutional character of the treatment, which varying from case to case, will overcome, or at least alleviate, his muscular weakness and enable him to enjoy his life as much as possible In many instances it will be necessary to induce him to make certain changes in his occupation if it becomes obvious that the amount of physical effort required for his job cannot be met even with the muscular

shown that 50 per cent of such patients can live a normal life when properly treated, and that 10 per cent can do this without any restrictions Even the more severe cases will derive comfort from the statement that remissions, sometimes of years, are by no means rare

It is desirable to evaluate the required prostigmine dosage by hospitalizing the patient for a week, thus enabling both doctor and patient to gain useful information during the therapeutic testing period It is recommended that observation be made as to the

strength

the onset

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tivity that can be gained by an intravenous injection of 0 5 mg or an intramuscular injection of 1 5 mg prostigmine methylsul

fate By this procedure the patient comes to understand how much benefit he can derive from the treatment and will be able to state whether the effect of consecutive treatment with prostigmine by mouth equals that by injection The administration of 0.5 mg prostigmine intramuscularly is about the same as that of 15 mg orally

Well worth consideration is H R Viets' idea of supplying every patient no matter how mild his disease with ampules of prostigmine methylsulfate along with instructions for emergency injections Likewise commendable is providing the patient with written information as to the necessary treatment for any physician or nurse who may be called in an emergency particularly in the case of respiratory difficulties Such

The average case of myasthenia gravis will be able to maintain comfort with 6 to 9 tablets of prostigmine daily and exceptionally mild cases may get along quite satisfactorily with the use of 2 or 3 The outstanding fatigue and weakness of the muscles used in swallowing indicate medication about 45 minutes before each of the three meals, thus assuring the usual intervals necessary for optimal effect Prostigmine is much more potent on an empty than on a full stomach, but also is more likely to produce unpleasant reactions such as anorexia epigastric distress, intestinal cramps nausea, diarrhea and even fainting spells In order to avoid many of these toxic stimulations of the smooth musculature, Eaton gave his patients a glass of milk and some crackers 15 minutes before the prostigmine Atropine

side effects of the drug An added complication is the ambulatory patient, who during his hospital observation may have been satisfied with 2 tablets of prostigmine before meals, but who will often need readjustment or increase of medication once he is on his own The physician may obtain considerable help by adopting Schwab and Skogland's method of evaluating the effect of treatment by requesting the patient to keep score of his condition—excellent, good, fair, poor, bad—on a chart four times daily Viets' suggestion not to change the schedule in the average case without an observation period of at least 2 weeks should be followed Before any unusual demand on his strength, the patient will do well to supplement his medication by taking an extra amount of prostigmine corresponding to that of his "before meal" dose, especially if this irregular effort occurs toward the close of day Night medication is required if the patient complains of nightly respiratory embarrassment or of early

enterically with salol, which would be resorbed with a delay of about 2 to 3 hours

Severe cases of myasthenia range from those in which oral medication cannot overcome the dysphagia sufficiently to prevent choking and aspiration of food to those in which respiratory failure is a constant danger to the frequently bedridden patient Treatment of severe dysphagia consists first in attempting to change the usual three meals a day to five to restrict mastication to a minimum by using a soft diet, and possibly to replace the oral administration of prostig

a nasal catheter will have to be instituted Respiratory disturbances may come on suddenly and are often preceded by anxiety states, which although relieved by prostigmine methylsulfate (1.5 mg), indicate threatening respiratory failure (Eaton) Such conditions may be controlled by hourly doses of prostigmine methylsulfate Viets has given 1.5 to 3.0 mg of this drug in 5 per cent dextrose by intravenous drip for a period of more than an hour The use of a respirator combined with oxygen can help save the life of such a patient Obstruction of the airway may necessitate a tracheotomy The anxiety and the undesirable motor restlessness call for sedation It stands to reason that all severe cases of myasthenia should be at complete rest Even so, the amount of medication necessary may be the multiple of that used in average cases Daily administration of 20 to 30 doses by mouth, frequently replaced by injections, may be needed, even

for periods of months and can still be followed by at least a partial remission However certain muscles particularly the external ocular muscles and the levator pal pebrae may remain more or less inactive even where prostigmine has helped the patient to a comfortable existence

Other drugs for the relief of muscular weakness in myasthenia are of minor im portance Ephedrine sulfate which is only about 10 or 15 per cent as effective as prostigmine (Viets) may be given exclu sively in mild cases two or three times daily in doses of 24 mg or less but administra tion should not be later than mid afternoon so as not to disturb the patient s sleep Quite a few patients like this drug and combine it effectively with prostigmine Potassium chlo ride has been found by physiologic experi ments to have great influence on the transmission of nerve impulses to muscle but its use is only rarely indicated It helps only a few and when given in sufficient doses (10 gm three times daily by mouth) its side effects are unpleasant Guanidine hydro chloride usually given three or four times daily up to a total dose of 10 to 25 mg per kilogram of body weight (Richter) may have a satisfactory effect on muscle fatigue but here again the drug has such unpleas ant side effects that most patients prefer prostigmine Gastro intestinal disturbances can be neutralized by atropine hyocine or belladonna but most patients interrupt this medication because of the disagreeable paresthesias around the mouth and at the finger tips the muscle twitchings and gen eral nervousness although alleviated by calcium gluconate *Diisopropyl fluorophos phate* has been tried lately by Comroe and

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larger doses produce unpleasant reactions on the part of the nervous system *Amino acid (amigen)* has been given by Torda and Wolff in combination with prostigmine and found effective Its practical use in critical prostigmine resistant conditions has yet to be worked out

Thymus Therapy Although the role played by the thymus gland in myasthenia gravis is obscure tumors of the thymus (15 per cent according to Good) as well as thymic abnormalities have been found in such a high percentage of cases (50 per cent according to Gillespie) that there is no doubt that the function or dysfunction of the thymus affects sustained muscle con traction Adams and Allan suppose that the mere presence of the thymus may be re sponsible for the myasthenia in sensitized individuals Thymomas usually benign are found much less frequently than hyper plasias which resemble hyperplastic lym phoid tissue similar to the findings in a toxic thyroid gland (Keynes Collins and Martin) The size of the thymus varying from 3 to 30 gm has been shown to have no relation to the severity of the disease (Keynes) Treatment with thymus extract has no spe cific effect

Thymectomy has been done since 1908 when Sauerbruch performed the first opera tion of this kind Adams and Allan have recently computed the results of 129 operated cases and found that 17 patients recovered completel 21 [illegible]

all or had died This would mean that 52 per cent were significantly benefited by thy mectomy Blalock and his co workers as well as Keynes call the results of the operative treatment encouraging

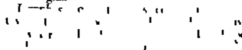
Since the operative risk is about twice the actual age of the patient (Adams and Allan) the selection of cases for operation is cer tainly a responsible task The risk is due partly to the difficulty of the operation itself especially in the presence of a tumor and partly to the character of the disease which with its threat to respiratory failure would make any major operation extremely hazard ous It is felt that patients with mild cases and patients beyond the age of 35 or 40 should not be operated on The presence of respiratory difficulties is a contraindication to the operation but once these are over come and a remission of several months has been established by prostigmine and rest therapy, such difficulties may not exclude the patient from surgery Every severe case of myasthenia in a young person should be treated with prostigmine in an optimal man ner for several months before thymectomy is considered Even then the possibility of spontaneous remission will raise doubts as

to the advisability of surgery The degree of the patient s lasting disability will weigh the scale in favor of thymectomy

As shown in the above figures the clinical results of the operation indicate that the majority of patients operated on still need medical care which means that cure is not established. Thymectomy for a thymoma verified by roentgen ray but without myasthenia gravis signs should be viewed with great reserve even though Murray and Mc Donald have stated that almost all patients with thymoma eventually develop myasthenia gravis

Irradiation of the thymus whether the gland is visibly enlarged or not, is still more difficult to evaluate as to success than thymectomy Eaton states that of 100 cases only *18 showed a remission during the ensuing* 12 months. But this statistical evidence may be misleading because as Eaton says cases too ill for an operation were included and the amount of roentgen irradiation given was often insufficient. Anna Hamann the well known radiotherapist, gives her experience with irradiation of the thymus as follows

In a small number of patients with myasthenia gravis encouraging results have been reported after roentgen and radium irradiation to the thymus gland.



thymic carcinoma is radioresistant and myxosarcoma is of moderate radiosensitivity

If the malignant nature of a thymus tumor is verified, intensive radiation with a total dose of 3000 r or more within the tumor is indicated. Though thymic enlargement caused by lymphosarcoma may completely disappear after a small dose of a few hundred r only the high total dosage is necessary for a lasting effect

Thymus hypertrophy may regress after small doses in the order of 600 to 800 r tissue dose in the thymus Therefore in patients with myasthenia gravis without demonstrable thymic enlargement or in cases with enlargement of

given at intervals of two to three months are safe

Roentgen therapy is administered as fractionated irradiation with daily surface doses of 200 to 300 r Two anterior chest portals are sufficient for moderate total dosage in the thymus while for high dosage in malignant tumors cross fire from additional posterior chest portals and supraclavicular portals is necessary

In lesions of moderate radiosensitivity regression of thymic enlargement and improvement of the muscular symptoms may be observed after 2 or 3 months only Improvement of muscular symptoms has been reported with and without demonstrable change in the thymus Adequate irradiation does not interfere with later surgery

While radiation therapy in the hands of an experienced radiologist is without risk, it has to be known that highly radiosensitive tumors may react with increased, potentially dangerous, swelling to excessive daily irradiation doses

There is evidence that in patients in whom thymectomy is contraindicated judicious irradiation by an experienced radiologist may be a *worth-while procedure*

Drug Contraindications First of the drugs to be avoided in myasthenia gravis is curare the effect of which on muscular contraction resembles the underlying pathology of myasthenia. Patients selected for curare treatment, whether in combination with shock therapy or for muscular spasticity should first be tested for curare sensitivity Bennett and Cash have shown that 1/10th to 1/5th of the average curare dose may precipitate muscular weakness even when given to non myasthenic patients and may cause possible respiratory difficulties in patients with a latent myasthenic condition. Thyroid medication increases myasthenic symptoms and signs and is of no help even in patients with a low basal metabolism. Eaton reports that, although hyperthyroidism complicated 6 per cent of his myasthenic patients thyroidectomy and the use of thiouracil were not beneficial in the average case Quinine is known to increase muscular weakness in myasthenia, and therefore a myasthenic patient with malaria should be given atabrine or some related drug that has no effect on myasthenia.

FREDERICK HILLER

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>
> Lymphosarcoma the most common malignant thymus tumor associated with myasthenia gravis is as a rule highly radiosensitive The hypertrophic thymus is also radiosensitive while thymic carcinoma is radioresistant and myxosarcoma is of moderate radiosensitivity
>
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DISEASES DUE TO ALLERGY

ALLERGY OF THE NOSE AND NASAL SINUSES

Allergy of the nose and nasal sinuses can best be discussed as it occurs, seasonally and perennially

Allergy of the nose and nasal sinuses is a frequent condition, characterized by edema of the mucosa of the nose and nasal sinuses

mon in rhinitis due to fungi, house dust, animal danders, etc

Bronchial asthma probably follows in about 40 per cent, but proper care from the allergic point of view will usually prevent the onset of asthma

Many individuals have both seasonal and nonseasonal rhinitis Some who think they have only hay fever will state on close questioning, that they have frequent "colds" which last a short time and are not infectious Such individuals usually give positive skin tests to both pollen and non-pollen allergens, e g, fungi house dust or feathers Nasal polyposis is uncommon in seasonal hay fever probably because the season is so short that the nasal mucosa cannot develop enough prolonged edema to force the formation of polyps In perennial rhinitis however, symptoms may be more or less constant with a much greater tendency to the formation of polyps If the polyps become large they may press on certain "trigger" areas with resultant attacks of asthma

In all types of allergy of the nose and nasal sinuses there is the fundamental allergic basis (see section on Bronchial Asthma) This is characterized by (1) a constitutional basis, usually by heredity, (2) contributory factors, such as mechanical dusts, chemical fumes, endocrine and psychogenic stimuli, and such physical agents as heat or cold, and (3) exciting allergens, e g, pollen fungi house dust, or foods

In all of these groups therefore, one usually finds eosinophilia in the blood and nasal secretion, a history of allergy in the family, or other allergy in the patient, and positive skin tests

The nasal smear for eosinophilia is extremely important and credit goes to Hansel who has emphasized its diagnostic significance The smear is best collected by having the patient empty his nasal secretion into a cellophane handkerchief The material is then fixed and stained (Wright, Giemsa or Hansel stain) Eosinophils in nonallergic cases should not exceed 4 per cent of the cells present In nasal allergy eosinophilia frequently reaches 50 or even 100 per cent —such high percentages are diagnostic of allergy If a patient with nasal allergy develops an infectious "cold" (acute coryza), the nasal eosinophilia will decrease or disappear and the cells in the nasal secretion will be chiefly polynuclear neutrophils after the acute "cold" is over, eosinophils will reappear and replace the neutrophils

Hay Fever (Pollenosis) "Hay fever is a seasonal condition caused only by pollen characterized by inflammation of the nose, eyes, and throat, often complicated by bronchial asthma Sneezing rhinitis, and conjunctivitis, with itching are usually present (Unger) It occurs in about 4 per cent of the population of the United States, probably less in other countries because of the absence of ragweed Asthma accompanies or replaces the hay fever in about 40 per cent of cases, and sinusitis and chronic bronchitis may also occur polyposis is rare, and emphysema seldom occurs in uncomplicated pollen asthma because there is ample time for restoration to normal before the next season

Etiology In general, in this country, the three hay fever seasons coincide with the

amount in the air of pollen of certain trees, grasses and weeds These light, buoyant pollens may be carried for long distances by the wind Pollen from flowers, on the other hand, are sticky and chiefly carried by in sects, and hence are of only local importance as causes of hay fever When the pollen count is high symptoms are apt to be severe in those who are allergic to the particular pollen When the pollen count is low, hay fever symptoms are usually mild or absent Asthma can, however, occur in stormy weather when the pollen count is low

In central and northern United States pol len from elm, maple, ash, oak, and other trees is in the air from about March to May or June Pollen from June grass, timothy, red top, and orchard grass abounds from the end of May to about mid July Giant and short ragweed pollen causes much suffering more than the other two combined, from about mid August to the end of September These dates are only approximate and depend on the weather and the location

Other important pollens come from Rus sian thistle Kochia, wormwood (sage), hemp, pigweed burweed marsh elder, cocklebur, and lamb s quarter Other sections of the country have other offending agents Grass, especially Bermuda grass is much more im portant in the south also west of the Rocky Mountains some sections have two grass hay fever seasons Mountain cedar pollen causes much hay fever around Dallas and San Antonio in December, January, and February Ragweeds are practically non existent west of the Rockies and outside of this country are found only in southern Can ada and northern Mexico with a few minor exceptions

For further details regarding pollen the reader is urged to consult Unger Durham and Vander Veer Much information can also be obtained from those who manufacture pollen extracts

TREATMENT Treatment can be divided into preventive, specific and symptomatic All three are important

Preventive Measures Children of allergic parents should be skin tested for pollens be fore they go to a camp where the pollen count may be high If the test is positive, they must not go to that camp while the particular pollen is in the air Once a pa tient's hay fever threshold (resistance) is overcome it may be difficult or impossible to restore it completely

Allergic individuals should not move to areas, e g, suburbs, where the pollen count may be higher Several of my patients have moved to suburbs which have many oak trees, and being sensitive to oak pollen they have experienced increase of symptoms Ad vice from a physician before moving may prevent suffering

Destruction of weeds automatically lessens hay fever To date there has been no con certed effort along this line though such action is highly desirable Pollen can travel more than 400 miles so that the problem is not too simple Perhaps the use of chemicals will prove more effective than have weed pulling and cutting

Filters are useful These can be installed in windows and most of these machines filter out 95 to 99 per cent of the pollen Nasal filters have been only mildly successful and most patients do not use them Places which are air conditioned are practically pollen free and similarly, pollen is almost entirely absent in rooms with shut windows

Avoidance of hay fever areas is of aid to those who can travel each hay fever sea son Those who are allergic to ragweeds obtain almost complete relief west of the Rockies and in Florida Those who are sensi tive to mountain cedar need only travel about 200 miles Those who are grass allergic may obtain relief above the timber line

Proper hyposensitization with pollen ex tracts almost always prevents the onset of asthma in that particular season

Specific Measures Specific measures have been used for many years, with considerable success, although complete elimination of symptoms is not usually obtained. *Hypo sensitization* usually prevents pollen asthma and usually lessens hay fever symptoms (ap proximately 75 to 85 per cent)

The pollen extracts must be carefully chosen, e g, patients who are allergic to ragweeds must receive injections of ragweed extracts, not of grass

Injections can be given preseasonally, co seasonally, and perennially Each method has its own function

The preseasonal method is most widely used The initial dose is usually 0 10 cc of

the 1 10,000 dilution injected subcutaneously but if the local reaction is large the initial dilution should be 1 100,000 or even 1 1 000-000 Each succeeding dose should then be

small doses e g, 1 10,000, most men do not give doses larger than 0 50 cc, 1 100 (The writer favors large doses, up to 6 per cent if the patient can tolerate such amounts His experience definitely shows that those who can take large amounts almost always obtain better results than those who develop reactions with smaller dosages)

Injections should begin as soon as the diagnosis is established The intervals of treatment should be adjusted so that the patient receives 25 to 40 injections if possible before the next hay fever season starts In the following schedule a typical preseasonal ragweed series is shown

SCHEDULE OF PRESEASONAL TREATMENT

Injection	Dilution	Dosage (in cc)	Injection	Dilution	Dosage (in cc)
1	1 100 000	0 10	17	1 1000	0 22
2		0 15	18		0 30
3		0 22	19		0 45
4		0 30	20		0 65
5		0 45	21		0 85
6		0 65	22	1 100	0 10
7		0 85	23		0 15
8	1 10 000	0 10	24		0 20
9		0 15	25		0 25
10		0 22	26		0 30
11		0 30	27		0 35
12		0 45	28		0 40
13		0 65	29	3 per cent	0 15
14		0 85	30		0 17
15	1 1000	0 10	31		0 19
16		0 15	32		0 21

In the above series, injections in the first two or three dilutions are usually given twice a week, the stronger injections once a week, then once in 2 weeks If there is plenty of time the injections may be started on a once a week schedule, instead of twice if rushed, the first injections should be given three times a week

During the hay fever season which follows this preseasonal treatment the dosages should be reduced about 25 per cent and given about once a week If severe hay fever is present the amounts should be still further reduced

After the hay fever season is over the perennial method begins Treatment is not

tinued until the next pollen season again lowered approximately 25 per cent during the season, and again gradually increased after the pollen is no longer in the air There are fewer reactions and better results by this method than can be obtained by repeating year after year preseasonal therapy

Co seasonal treatment is advised for those

repeat this daily or every other day for three injections, then increase to 0 04 cc. for 1 or 2 injections then 0 06, 0 08, and 0 10 cc The results are sometimes surprisingly good The usual preseasonal dosages are given after the hay fever season is over, followed by perennial treatment

By these methods better results for each patient are usually obtained each year, then injections may be stopped in some cases Unfortunately, there are some depressing exceptions in which hay fever seems to occur year after year, despite what we deem sufficient and correct therapy

In pollen asthmatic patients treatment should not be stopped but should be continued at 2 to 4 week intervals year after year It has been our experience that such treatment usually prevents or markedly lessens asthma We have also found that asthma almost always returns the first season for which injections have not been given and such asthma is frequently so severe as to necessitate hospitalization

Excellent durable pollen extracts can be made with glycerin, and short lasting solutions with sodium chloride The best extracts, in the writer s opinion are those made with dextrose These extracts are clear, stay potent as long as those made with glycerin, and, above all do not sting or hurt on injection Our formula is

Dextrose, C P	45 gm
Phenol C P	5 gm.
Sodium bicarbonate, C P	2 gm
Distilled water to make 1000 cc	

Local and general reactions can occur If there is much local inflammation the preceding dosage is either repeated or reduced This precaution usually prevents constitutional symptoms which would almost certainly occur if dosages were increased But if asthma, hay fever, or urticaria should occur as a result of an injection, the patient should receive epinephrine 0 5 cc of 1 1000 dilution subcutaneously and/or aminophylline 250 mg intravenously, and his next dosage should be sharply reduced All patients should sit in the doctor s office for at least 15 or 20 minutes after injections of these extracts and the site of injection should be inspected before the patient departs A tourniquet should be used for 5 or 10 minutes above a severe local reaction *Itching of a hand after an injection is a definite warning that any further increase in dosage probably will bring on a constitutional reaction* With care our percentage of reactions has been markedly reduced

Oral pollen therapy has been used by some but it has rightly fallen into disuse The results are poor as compared to those obtained by injections, and severe gastro-intestinal symptoms have occurred

The mechanism of hyposensitization is not too clear although considerable success is obtained in most cases The role of the 'blocking or inhibiting antibody of Cooke is uncertain This new antibody is found in patients who have received a series of injections of pollen extracts but it is also found in normal persons who have been given similar injections

Failures from hyposensitization usually result from incorrect choice of pollen extracts, or to dosages which are too weak or too strong for that patient, or to the use of deteriorated extracts or to the failure to test for and to remove during the hay fever season extrapollen substances which aggravate symptoms

Symptomatic Treatment Symptomatic treatment of hay fever is also important, especially since the recent introduction of the new antihistaminic drugs Up to that time our symptomatic measures were not too effective The large number of available medicines and methods demonstrated the uselessness of most of them

Ephedrine, locally and by mouth gives some relief It makes patients "nervous" and should be combined with a sedative, e g, seconal The more one uses "nose drops" the less one is impressed, *though there is no* objection to the occasional use of a nasal vaporizer or of an ephedrine or similar jelly to relieve severe nasal blocking Neosynephrin in 0 25 per cent solution is about as effective as ephedrine, and many pharmaceutical firms have other drugs of similar nature

For many years our patients have been helped by the following prescription for the conjunctivitis of hay fever

Epinephrine hydrochloride	min xv
Dilute acetic acid	min v
Resorcinol	gr iii
Distilled water q s ad	℥ i

Fac solut Sig One drop in each eye as nec for hay fever

Operative treatment for hay fever is usually unsuccessful, but, if indicated for infectious sinusitis or markedly deviated nasal septum, the procedure should not be carried out during the hay fever season Nasal cauterization is now rarely done, and removal of tonsils and adenoids does not help hay fever, if indicated for other reasons it, too, should be performed outside of the pollen season

The new antihistaminic drugs constitute a definite aid in the treatment of all kinds of allergic rhinitis Benadryl (B dimethylamino ethyl benzhydryl ether) and pyribenzamine (pyridil N' benzyl N dimethyl ethylene diamine) are the most widely used in this country Other members of this group include antergan, neoantergan, antistin, theophorin thenylene, neohetramine, histadyl, and others

All of these drugs are supposed to neutralize the effects of histamine, and they all do this to a greater or lesser extent, both in experimental animals and in man However, they have little effect in lessening the output of gastric juice brought on by an injection of histamine Ratner, whose views are shared by many, concludes that the release of histamine has not yet been proved to be the fundamental factor in anaphylaxis or allergic reactions, hence any therapy based on such a concept must be called into question

All of these "antihistaminic" drugs have now received considerable trial Benadryl

and pyribenzamine have been most widely used, and the results in all types of allergic rhinitis have been about the same This statement also applies to the other drugs of this group All have successfully lessened itching of the eyes and nose and have de creased nasal blocking and rhinorrhea They also lessen pruritus, and are useful in urticaria and angioneurotic edema They are of much less help in bronchial asthma and in atopic dermatitis ("eczema")

All of these drugs have some disagreeable side effects, disagreeable but not dangerous

The usual dosage in hay fever is about 50 mg every 3 or 4 hours, if and when symp toms occur. Some use these drugs prophylactically, others give them only when symptoms are present Relief may last a few hours (Feinberg)

I agree entirely with Friedlaender and Friedlaender, who state "The antihistaminic drugs are purely palliative medication They produce no lasting benefit and possess no curative effects Chronic symptoms usually recur a short time after withdrawal of the drugs . . Inasmuch as the effect of a single dose is of relatively short duration, they should only be employed where active symp toms warrant their use The use of these drugs is not a substitute for the careful im munologic study necessary in each case of allergy The determination of specific etio logic factors, the elimination of the offending allergens where possible, or hyposensitization when necessary, are the sole means at present of achieving lasting results in allergic disease The antihistaminics are valuable symptomatic drugs which may frequently afford the patient temporary relief from his discomfort until the effects of more specific therapeutic measures become evident"

The use of hapamine (histamine azopro- … They are

recent years there has been a decidedly increased interest in the role of inhalant fungi, espe cially molds and smuts Large numbers of patients develop rhinitis and/or asthma year after year from this type of allergy, just as many others are affected by inhalation of pollen, and others from both fungi and pollens The important fungi are discussed in many references, especially by Feinberg and Unger There are thousands of different kinds of fungi and our knowledge is still fragmentary, but enough is known about them to warrant the following statements

(1) They abound in the air all year round, especially in warm weather They are present, but in much fewer numbers, in winter

(2) The total fungus counts are apt to be high in some places and low in others According to Durham, for example, the total mold spore count in Phoenix, Ariz (1933) was only 160, and only 191 in New Orleans, whereas it was 17 280 in Springfield, Ill (1940), 17,131 in Moorhead, Minn (1937), and 16,139 in Dallas Much territory needs to be surveyed, and we know that mold counts vary with the weather even more than do pollen counts

(3) In some localities fungi cause more suffering than pollen For example, in 1948 in Chicago we found on our exposed slides approximately 4 000 tree, 1,000 grass, and 5 000 ragweed pollens (total counts) By comparison, we counted over 20,000 molds and smuts, chiefly Hormodendrum and Alternaria molds And, clinically, too, our impression was that suffering in 1948 came much more from fungi than from pollen This was not true in other years, especially when there was a high ragweed count (up to about 13,000)

(4) The action of these inhalant molds and smuts (and yeasts to a much lesser extent) is like that of pollen—they act as allergens They probably have no bacteria-like effect, as opposed to those fungi like Actinomyces which may be pathogenic Since they act as allergens, they give almost as good positive scratch tests as do pollens, and are likewise positive in sensitive patients on testing by the intradermal, nasal, and conjunctival methods, also by passive transfer

(5) The two most important molds in the central part of the United States are Alternaria and Hormodendrum Durham concluded that "the largest Alternaria belt extended from the Rockies to the Appalachians, both coasts and the deep South being comparatively free ' These molds are

found chiefly from May to October, and are especially common in late July and early August, between our grass and ragweed seasons. (Therefore if a patient has rhinitis or asthma at this particular time each year, he is apt to be allergic to Alternaria.) Hormodendrum, on the other hand, is probably found all over the world and is less limited as to season. Other molds which may cause symptoms and which are used in extracts for hyposensitization are: Aspergillus, Penicillium, Helminthosporium, Mucor, Monilia, Phoma, Fusarium, Botrytis, Rhizopus, Chaetomium, Cephalothecium, and occasionally others.

(6) The mold spore is the reproductive body and represents the allergenic part; extracts made from spores are usually potent and give good positive skin tests and can give local and systemic reactions in sensitive individuals. Extracts made from mycelia are of little value in testing or in treatment. Mold spores, like pollen, are light and small, and are wind borne and can be carried for long distances as shown by Durham, who reported the transportation, during a 1937 windstorm, of large numbers of spores from southern Minnesota to various parts of the eastern seaboard and to the Gulf of Mexico.

(7) Molds are counted by the exposed slide method as carried out for pollens. Mold colonies are also counted by culturing in Petri dishes. Not all molds can be identified by both methods.

(8) Smut grains can often be seen on exposed slides. Corn smut resembles a small ragweed pollen. They are especially common in showers in the summer and fall. They grow poorly in cultures. Corn smut is the most important, but smuts from wheat, rye, barley, oat, and Johnson grass may also cause symptoms, especially in farmers or in those who live close to farms, or in those who handle cereals (grain mill workers) (Wittich). Smuts are probably the most allergenic factor in allergy from "farm dusts"; these dusts are important causes of asthma and rhinitis. Mites and other insects, the cereals themselves, and certain feeds may also harass the farmer. In our office we usually treat these patients, after positive skin tests to the mixed farm dusts and the individual components, by injections of a mixed farm dust extract.

(9) Yeasts often give positive skin tests, but more often in atopic dermatitis than in respiratory allergy. They are important enough to use in hyposensitization, as well as to avoid, as in bread, crackers, coffeecake, beer, and certain vitamins.

(10) Rusts from wheat are found on exposed slides. Cadham reported 3 cases of asthma supposedly due to inhalation of these rusts, but his findings have not been confirmed.

The diagnosis of inhalant fungus allergy is based on the usual history of seasonal symptoms which are increased with high fungus counts and lessened with low counts. In addition, skin tests are usually positive (scratch more reliable than intradermal), and other evidences of allergy are usually present.

In addition to atmospheric fungi, respiratory allergy may be caused by molds which grow in old bedding, in damp basements, on "moldy" articles, and on or in articles of food, e.g., tomatoes, bread, or cheese. Symptoms in such cases come at any time of the year—they are not seasonal.

Treatment of mold allergy is similar to that with pollen. Since mold seasons are longer it is more difficult to give injections preseasonally, but when possible this method beginning with about 1:10,000 or 1:100,000 is to be used, followed by co-seasonal and perennial treatment, as with pollen. If the patient reports during the season, dosages should be small and increased cautiously. Local and general reactions can occur, as with pollen.

The choice of the particular fungus extract is not always easy. It should depend on the correlation of symptoms with atmospheric counts and also, to a lesser extent, on skin test reactions to individual molds or smuts. Since Alternaria and Hormodendrum are probably responsible in 70 to 75 per cent of these cases they should make up the largest percentage of the extract. The other fungi are then added to make 100 per cent. If, however, there is strong clinical and skin test proof that the symptoms are due to *Aspergillus fumigatus* or to Penicillium or to corn smut, the particular allergen should be chosen, and the others may or may not be added. Some allergists routinely add about 10 per cent house dust extract to these

fungus extracts and add about 10 per cent in-

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as with pollen, i e, about 75 to 85 per cent of all patients receive more or less benefit and in over 90 per cent a previous asthma from fungi does not recur The writer is particularly impressed with the brilliant results usually obtained from injections of mixed farm dust extracts (largely smuts) in farmers and those who live close to farms This is in line with our findings that we almost always have good to excellent results if we hyposensitize with an extract derived from the premises in which the patients have symptoms, e g, dust derived from the bakery, furrier, or upholsterer

e g, Tucson and Phoenix, and perhaps this fact explains the good results which some patients have on moving to that region Damp basements should be dried by calcium chloride sacks

Avoidance of smuts may involve leaving a farm, but hyposensitization usually suffices

The symptomatic treatment of nasal allergy due to fungi is similar in most respects to that of pollen hay fever Conjunctivitis, however, is not nearly the problem with fungi that it is with pollen

Allergic Rhinitis (Perennial, Vasomotor, Hyperesthetic) This is a common condition, already discussed to some extent Its etiology and treatment are similar to those of bronchial asthma with which it is commonly associated Few patients with asthma fail to have a preliminary or concomitant allergic rhinitis

Allergic rhinitis, probably the best term, frequently is called sinusitis or just "sinus At least 75 to 80 per cent of all so called "sinusitis' is due to allergy, as can be shown by the findings of allergy. heredity, nasal and blood eosinophilia, positive skin tests and relief from avoidance with or without hyposensitization

The exc

cause, along with feathers, orris root, occupational dusts, cottonseed, and animal derivatives Allergy to foods can also cause allergic rhinitis

Infectious rhinitis should be easily differentiated from allergic rhinitis, especially by the absence of eosinophils in the nasal smear and the absence of other evidences of allergy (Hansel and Chang)

The treatment of allergic rhinitis is both specific and symptomatic The specific measures are careful avoidance of the allergens, with or without hyposensitization, as with bronchial asthma Good results are obtained in most cases, although much depends on the co operation of the patient in removing or lessening exposure to house dust, etc

The symptomatic treatment is similar to that outlined Nose drops are used by some, ephedrine jelly temporarily opens blocked nostrils The new antihistaminic drugs, e g, pyribenzamine and benadryl, give good symptomatic relief in most cases but their use should never supplant specific allergy measures, including skin tests

Surgical treatment is of little avail although marked polyposis should be taken care of, also severe nasal obstruction due to a deviated septum Sinus surgery should be reserved for infection only Cauterization and ionization now are rarely done Autogenous or stock vaccines are probably of some value, even when there is no definite evidence of infection Also, it is important to combat contributory factors, e g, psychogenic, mechanical, estrogenic, or infectious

The results of treatment in allergic rhinitis are about on a par with those obtained in asthma The most successful cases are those in which the exciting cause can be found and removed The least successful are in that group in which the skin tests and nasal smears are negative, and especially in instances in which menstrual disorders seem to play a part The administration of thyroid extract may help in those cases in which there is a lowered basal metabolic rate

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BRONCHIAL ASTHMA

Bronchial asthma is an allergic condition, occurring at any age, paroxysmal or chronic, characterized by wheezing, dyspnea, orthopnea, and cough, usually associated with rhinitis and with partial obstruction of the lower air passages

Environment is important from the therapeutic point of view, especially as regards exposure to large amounts of house and oc-

TABLE I

OCCUPATIONAL ASTHMA AND RHINITIS

Occupation	*Chief Allergens*
Aquarium supplies	Derris root, water flea (fish foods)
Bakers	Wheat, corn, rye, buckwheat, spices
Barber (and beautician)	Orris, root, henna, dyes, karaya (Indian) gum, tragacanth, flaxseed, quince seed, hair, sheepwool, wool grease, oil of citrus group, essential oils
Bedding	(1) Feathers chicken, duck, goose, swan, pigeon, turkey
	(2) Animal hair horse, rabbit, goat, cow, hog, cat, sheep
	(3) Cottonseed, kapok, silk floss, flaxseed
	(4) Straw, corn husks, wood shavings
Brushes	Animal hair cow, hog, horse, goat, sheep
Butchers	Hair cow, sheep, hog, rabbit
	Insecticides, preservatives
	Boxwood (sawdust) on floor
	Physical allergy (cold refrigerators)
Canners	Peas and beans infested with Indian meal moth
Clothing	Dyes
	Hair horse, goat, cattle, cat, dog, rabbit, camel, sheep wool
Exterminators	Pyrethrum, orris root, chemicals (DDT)
Farmer	Vegetables (tomato workers Cladosporium), cereals, etc
	Livestock and cats, dogs, rabbits, etc
	Poultry
	Corncockle
	Chicken coop mites, molds, smuts, feed (kamala)
	Pollen, molds, corn dust (smut)
Florist	See Horticulturist
Flowers (artificial)	Feathers chicken, duck, goose, swan, turkey
	Silk
	Dyes
Flour Mill Workers	Grain smut and rust
	Wheat, rye, corn, buckwheat
	Molds, mites, pollen
Furniture	See Bedding
Furriers	Dyes
	Insecticides, sawdust (boxwood), furs
	Fumes from cleaning fluids e g, naphtha

TABLE I—(*Continued*)

Occupation	*Chief Allergens*
	Imitation furs cat, dog rabbit, goat, cow
Gloves	Hair rabbit, horse, sheep, goat, cat
Grain Elevator Operator	See Flour Mill Workers
Grocer	Coffee dust Flour dust Spices Boxwood (sawdust) on floor
Hat Maker	Fabrics cotton, wool, silk, furs Feathers duck, goose, ostrich chicken, pigeon Hairs horse, goat rabbit, sheep Bleaching agents banana oil, oxalic acid, dyes
Horticulturist (Florist)	Flowers of all kinds Holland bulbs wormwood Hay, straw, grass mats, Pyrethrum Molds and fungi May and caddis flies other insects
Housewife	House dust feathers orris root pets Pyrethrum (insecticide), DDT
Insulators	Animal hair goat rabbit, hog Flax and straw
Jewelers	Boxwood (sawdust) Cuttlefish bone Orange stick
Laboratory Worker	Hair guinea pig rabbit, dog cat horse mouse sheep
Metal Polishers	Rouge, resin bichromate, oxalic acid turpentine
Painters	Linseed oil dyes, lead
Pharmacist	Acetylsal acid Arsphenamine Caroid Cocaine Codeine Dichloramine T Ipecac Lycopodium Methyl salicylate Peptone Podophyllin Poke root Pyramidon Quinine Rhubarb Urease
Poultry	Feathers chicken, duck, goose, turkey Chicken feed linseed, castor bean soybean Mites smuts and rusts kamala powder
Printers	Acacia (offset spray), dyes glue
Rag Sorters	Wool, cotton silk, linen Dust Insects
Refrigeration	Sulfur dioxide

TABLE I—(*Concluded*)

Occupation	*Chief Allergens*
Rugs	Animal hair cat, rabbit cow, sheep, wool, camel, goat Lead Dyes
Shoe	See Glove
Tobacconists	Tobacco (?) Perfumes Flavorings Gum tragacanth
Tomato Workers	Cladosporium (mold)
Toys	Animal hair cat, rabbit cow, sheep goat, dog horse Lead Dyes Glue
Warehouse Workers	Coffee Dust Cocoa Flour smuts and rusts molds Insects
Wig Makers	Animal hair goat horse sheep See also Barber

Three main etiologic factors are important in bronchial asthma, especially the third These factors must be discussed because of their extreme importance as related to the treatment of the asthmatic patient

(1) The constitutional basis is unknown, but heredity plays a large part, with a positive family history of one or more allergic conditions in at least 60 per cent of cases The stronger this factor, the earlier is an allergic condition apt to develop in the children, a fact which we use to advantage in preventive treatment In those whose asthma begins after 40, the hereditary factor is much less important

(2) Contributory factors rarely, if ever, act as sole causes of asthma, but they may aggravate or incite attacks in allergic patients who are also exposed to the various exciting allergens listed in the next paragraph These contributing influences may be mechanical, e g, chalk and other dusts, chemical fumes of all kinds, various physical agents such as cold, heat, light or pressure, infections, especially the ordinary "colds", and psychogenic and endocrine stimuli Since they aggravate symptoms they must be considered in treatment

(3) Exciting substances (allergens) are the stimuli which bring on the attacks in sensitized persons They usually act by inhalation, but can also act by ingestion or by injection The chief allergens in bronchial

asthma and perennial (allergic) rhinitis are

(A) Inhalants
- (i) Pollen of trees, grasses, weeds
- (ii) Fungi mold spores, smuts, rusts, yeasts
- (iii) Animal hair, dander, feathers
- (iv) House dust
- (v) Cereals flour of wheat, corn, etc
- (vi) Seeds of cotton, kapok flax, etc
- (vii) Miscellaneous orris root (cosmetics), Pyrethrum (insecticides), karaya gum (wave sets), certain powdered drugs, etc
- (viii) Occupational dusts, e g, farmer, miller, furrier, baker, upholsterer, domestic

(B) Ingestants
- (i) Foods egg, wheat, milk, fish, pork, etc
- (ii) Drugs, especially aspirin

(C) Injectants
- (i) Overdose of extracts used in hyposensitization, especially pollen
- (ii) Drugs, e g, morphine, arsphenamine, and vitamins
- (iii) Serums, e g, tetanus and diphtheria antitoxin

(D) Miscellaneous mode of action not too clear
- (i) Bacteria and their products,—these important but not known whether primary or secondary in action
- (ii) Parasites e g, Ascaris and taenia
- (iii) Silk
- (iv) Physical agents, e g, cold or heat

Space will not permit further discussion The etiologic factors are so important that the reader is urged to consult books and articles on this subject

Cooke's postulates must be observed (1) the causative allergen must give a positive local reaction or must be able to cause the clinical symptoms, (2) the patient must have been exposed to this substance

Pathogenesis As Related to Treatment. Symptoms of asthma are almost always due to partial obstruction in the lower air passages We now know that edema is the main factor, edema in the walls as well as in the lumina Some of this watery fluid is exhaled and this often leaves behind thick tenacious sputum and pieces of mucus which obstruct breathing In addition, there is often an increased secretion of mucus in asthma and in some cases spasm of the bronchial muscles may also occur All of these factors tend to increase the difficulty and cause the lowered vital capacity always more or less present in bronchial asthma In chronic asthma hypertrophy of bronchial muscles, as shown by Huber and Koessler, may still further lessen air space

Histamine or a histamine like substance is thought by many to be elaborated during attacks of asthma by interaction of allergen and antibody in or at the sensitized bronchial cells Despite many experiments this theory has not been proved, and there is much evidence against the hypothesis The recently discovered "antihistaminic" drugs e g, benadryl and pyribenzamine, have been almost totally ineffective in all but the mildest cases of bronchial asthma Some of the recent literature on this subject has been discussed (Unger, Unger and Gordon)

Death in asthma is uncommon but it does occur, especially when morphine has been given in chronic asthma This drug has no place in the treatment of bronchial asthma, as emphasized in Table II

TABLE II

CAUSES OF DEATH IN BRONCHIAL ASTHMA

1 Asthma main or sole cause	21 cases *
2 Asthma a contributory factor	16 cases
3 Other causes (asthma not a factor)	11 cases

Cause of Attacks Treatment in asthma and other allergic conditions gives best results when the cause of attacks can be found and can be partially or wholly removed It is essential, therefore, to use every possible method and all clues to discover this cause

Histories must be thorough and the patient must be permitted to talk without interruption Removal of suspected factors

*Morphine known to have been injected prior to death in 6 of these patients

may relieve symptoms, re exposure may bring on attacks Correlation of symptoms with seasonal pollen and fungi counts is also important

Skin tests should be thoroughly carried out, first by the scratch method Intradermal tests should then be made if sufficient information has not been obtained Skin tests only give clues, all positive reactions must be clinically correlated

Therapy. Treatment is divided into preventive, specific, and symptomatic (nonspecific) aspects All are important

PREVENTIVE Preventive measures apply especially to children of allergic parents, since they are more apt to develop asthma and other allergic conditions than do children of nonallergic parents The following points are important

(1) These children should be shielded from the most common allergens, e g, cats, dogs, feather or kapok pillows and comforters, fuzzy toys, and orris root (certain cosmetics) Damp basements may be full of molds Pollens abound in vacant lots and at many day camps Therefore these children should have tests for pollens before they go to camps New foods should be added to the diet one at a time, a week apart, to see if symptoms result Raw eggs should never be

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raw foods The home should be clean and no dusting permitted, a good vacuum cleaner, with attachments, is essential

(2) Should mild allergic symptoms occur, a thorough allergy survey should be carried out at once Children rarely "outgrow" asthma or other allergic conditions, it is easier to prevent chronic asthma than to

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out the wheeze), hay fever, perennial allergic rhinitis, urticaria, and various types of gastro intestinal symptoms which, in these ch

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should also be undertaken, if avoidance can not be complete

(3) Allergic persons and their children should avoid "dusty" occupations (Table I), especially those of farmer, furrier, baker, upholsterer, domestic, and grain mill worker

(4) We advise against intermarriage of allergic individuals but when love dictates, this advice is usually ignored However if a healthy person inquires regarding a prospective marriage to an individual who has moderately severe or severe chronic bronchial asthma, I believe it is the duty of the physician to point out that further attacks are likely, that social and other activities may have to be curtailed, and that nocturnal symptoms are common, with resultant loss of sleep

(5) Good nutrition and other hygienic measures are important especially as regards avoidance of persons with ordinary infectious "colds" Such "colds" are apt to bring on severe asthma, but only in allergic persons

SPECIFIC TREATMENT Our best results in asthma and other allergic conditions are obtained in those whose offending allergens have been discovered and can be removed If such avoidance cannot be complete, hyposensitization is necessary, this is a measure which usually raises the patient's resistance so that he can withstand ordinary amounts of the causative factor Many patients become symptom free, but permanent immunologic "cure is rarely possible, as shown by recurrence of symptoms on re exposure to dogs, cats, or eggs, and by skin tests which usually remain positive even with no symptoms

Elimination if complete, leads to relief from symptoms in paroxysmal asthma, although one cannot expect such an excellent result in patients who have chronic asthma with such complications as emphysema, atelectasis, or bronchiectasis

tain wheat Halfway measures often fail Diet lists are essential, and at each office visit the patient is questioned as to possible exposures to a food allergen

Those who are allergic to inhalant substances should also receive written instructions Their homes should be as nearly allergen free as are most hospitals No dogs or cats are permitted, even if skin tests to

these are negative Dust free covers or rubber bedding is advised in almost all cases Good vacuum cleaners with attachments are to be ordered, also *linoleum bottoms to all* soft furniture so that dust cannot fall to the floor Nonallergic cosmetics are advised The more thorough the elimination the better are the results

Hyposensitization (*desensitization*) consists of injections of increasing amounts of extracts of important allergens which cannot be avoided, e g , pollens fungi, house and occupational dusts orris root animal danders, and cottonseed The oral method is occasionally used, but is not entirely successful

The technic is described in detail in Unger's *Bronchial Asthma* Briefly, injections are begun with weak dilute solutions and are increased approximately 50 per cent with each injection with due regard to local and general reactions The injections are usually given twice a week at first, later once a week, and then once in two weeks or even three or four weeks

The opening dilution is usually based on the size of the skin test to the particular allergen If the reaction to the scratch test is 4 + it is best to begin with 1 1,000,000 or even weaker If the reaction is smaller, one can usually *start with* 1 10,000 or 1 100,000 The final dilution varies with different allergists A few give only the weaker dilutions, but most men continue to increase to as strong an extract as the patient can tolerate

A typical dosage schedule is that which we use in hay fever (see section on Hay Fever) In that section, too, are remarks regarding frequency of injections and a consideration of local and general reactions

Injections in asthma are usually continued for at least a year, longer if symptoms persist From time to time the patient's condition is checked If he is not doing well several procedures must follow (1) Skin tests should be repeated, especially if asthma occurs during a pollen or mold season or if a new clue is unearthed (2) The patient's home must be inspected to see if he is actually carrying out the instructions advised at the time of the first allergy survey, many patients are careless or unco-operative (3) A trial in an asthma room in a hospital is often of great help in lessening symptoms (4) Some new type of therapy may be instituted, e g , a new drug or a vaccine or *other nonspecific measure*

Symptomatic (Nonspecific) Treatment By the measures now to be discussed we seek to relieve the patient's symptoms We do not expect to prevent all further attacks of asthma, that is the function of the specific treatment just discussed

Symptomatic treatment can best be discussed as we see the patients, i e , in their homes, in our offices, and at the hospital Certain measures are common to all

(1) Reassure the patient The attack of asthma may be the first or may be so severe as to frighten the patient and the family The physician should at once state that the attack will subside (and it almost always does) Death is rare in uncomplicated asthma unless morphine is injected Urbach was correct when he said "The asthma doctor must and dare not forget that his own quiet, deliberate and reassuring manner and his absolute conviction that almost all cases of asthma can be cured constitutes one of the most important prerequisites for success"

(2) Restrict the patient's activity in accordance with the degree of the asthma Some anoxia already exists, needless exertion only increases symptoms

(3) Aminophylline, given intravenously,

sure or pulse rate The drug is also useful when given rectally (10 grains in 20 cc tap water) or in 7½ grain (0 50 gm) suppositories *By mouth it is of little use, and because* of painful local reactions we do not inject the drug intramuscularly

(4) Epinephrine can be given in doses of 0 50 cc of the 1 1000 solution, intramuscularly in oil (1 500), and/or by inhalation (1 100) This drug also gives excellent results in most cases of asthma and is preferred in children It should not be used in patients who have already had too much epinephrine (epinephrine fast), as shown by pallor, tachycardia, and tremor It may be used in hypertension, but with caution and in small amounts

(5) Ephedrine in doses of ⅜ to ½ grain (0.25 to 0 32 gm), orally, is useful in mild

nd moderate asthma Its effects are like hose of epinephrine, with similar precau ions It is usually combined with a sedative, g, ephedrine seconal

(6) *Morphine should never be used in ronchial asthma*, it is too dangerous It lows respiration and lessens the cough relex and the expulsion of sputum thereby ncreasing anoxia Its use frequently precedes xitus

Treatment of asthmatic patients in the home must be prompt and correct The following measures are recommended

(1) Reassure the patient (see above)

(2) For adults give 10 cc aminophylline (3¾ grain or 0 24 gm) intravenously at once The patient's arm should be horizontal a good light is essential and the injection should take about 4 to 5 minutes A 25 gauge 1 or 1¼ inch needle is advised with a 10 cc all glass eccentric syringe Nausea and vomiting will usually occur if the injection is given too rapidly

(3) Then inject 1 0 cc of the 1 500 epinephrine in oil in the outer upper quadrant of the buttock, with precautions as with all oily preparations

These two measures will usually break up an attack or give some measure of relief Larger doses of aminophylline are not recommended *The injections may be repeated in* 8 to 12 hours, if necessary (The author urges all physicians who make house calls to pack in their bags the following two or three 10 cc glass syringes with long thin needles, two or three 2 cc glass syringes, with wider needles, two or three 1 cc syringes and hypodermic needles several 10 cc ampules each of aminophylline and 1 0 cc ampules of epinephrine in oil and a 30 cc bottle of 1 1000 epinephrine solution The syringes and needles should be individually wrapped in paper and dry-sterilized (autoclave or oven) They are then quickly available when the patient is short of breath and the physician is short of sleep)

After the patient has been more or less relieved the physician should check the home for possible clues to attacks, e g, a dog or cat, kapok or feather pillows or comforters, horsehair mattresses, excess house dust etc At that time he should urge prompt skin tests and other detective measures, if not already carried out The physician should not be content merely to check attacks because if he does that alone the patient will often learn to treat himself and is much more likely to become a chronic sufferer than if examined from the allergy point of view If the physician is not equipped for this allergy survey he should refer the patient to an allergist and the allergist should make the tests and send the patient back with the necessary suggestions for treatment By this combination the patient will usually receive the best possible therapy

A subcutaneous injection of 1 1000 epinephrine (0 20 to 0 40 cc) should be given to children followed by about 0 50 cc of 1 500 epinephrine in oil In addition, we recommend syrup of ipecac, 1 teaspoonful every hour until vomiting occurs because expectoration of sputum usually accompanies emesis It is in these children, especially, that prompt allergy surveys usually give excellent results

Treatment in the office does not differ materially from that in the home For severe attacks we give 0 24 gm aminophylline intravenously (slowly), followed by 0 50 to 1 0 cc epinephrine in oil (buttock) We also

tum, apomorphine is an excellent expectorant)

Apomorphine hydrochloride	2 grains
Potassium iodide	5 drams
Syrup cherry q s ad	4 ounces
Sig 1 teaspoonful four times daily	

At the office too the examination, fluoroscopy and laboratory and skin tests are carried out and these procedures are followed by the necessary injections of various extracts e g, ragweed or house dust, plus dietary and other instructions

Treatment in the hospital is necessary for those patients who do not clear up at home and for those who have complications The reader is urged to prepare in his own hospital at least two or three rooms for this purpose Wesley Memorial Hospital (Chicago) has 12 beds especially designed for severe asthmatic patients Filters in the windows over radiators clean the air and warm it in cold weather The bedding is sponge rubber

or fiber glass The floor is covered with in laid linoleum Each room contains 2 steel chairs with large dust proof leather cushions Thin curtains are replaced every 2 weeks Flowers smoking and dusting are forbidden in these rooms only wet mops are used

Almost every patient whose asthma is due to inhalation of an allergen is quickly re lieved in one of these rooms If his symptoms are still present after 4 to 7 days he is prob ably allergic to a food or has some bacterial or other complication Such rooms are there fore invaluable not only for treatment but also for causative differential diagnosis An asthmatic patient commonly enters the hos pital with severe asthma After a few days in one of these asthma rooms he goes home asthma free After a few days at home his asthma recurs and is relieved when he re enters the hospital Something in his home is the offending agent usually house dust a pillow or an animal It is therefore impor tant to clean up the patient s home from the allergic point of view while the patient is in the hospital This procedure usually gives excellent results provided the home is made almost as dust free as is the average hos pital Bare floors or linoleum covered are

Oxygen inhalation is indicated in cyanosis or great weakness It is of little use in simple asthma Helium may be added but is seldom used

Glucose is indispensable in asthma it may even have a specific effect Epinephrine forces glycogen from the liver and the glu cose is doubly necessary for patients who have received much epinephrine We give glucose intravenously and each patient also receives 5 oz daily of glucose in the form of Dyno (Ratner) dissolved in a quart of fruit juices This mixture is nourishing too an im portant consideration in many of our asth matic patients

An instillation enema of 2 oz of ether and 4 oz of mineral oil may relieve severe spasms of asthma A full ether anesthesia (30 to 40 minutes) may favorably terminate severe asthma (Unger)

The diet should be ample If the patient cannot eat much because of dyspnea he should be encouraged to take frequent small meals

Chemotherapy is not indicated in simple asthma but is if infection complicates the picture as shown by leukocytosis crepitant rales increased sedimentation rate and/or fever with or without abnormal findings in

While in the hospital the patient also re ceives therapy similar to that given at home Aminophylline however is usually mixed with glucose by intravenous drip For the first three days we usually inject once a day 0 48 gm of aminophylline in 1 liter of 5 per cent glucose in water at 60 drops per min ute This procedure plus 1 0 cc epinephrine in oil twice a day intramuscularly plus iodides and apomorphine usually relieve at tacks

If however asthma persists other meas ures become necessary "Continuous amino phylline by intravenous drip is usually successful (Goodall and Unger) The needle is left in the vein and 1 0 to 1 5 gms of aminophylline are instilled with 1 liter of 5 per cent glucose at 28 drops per minute (2 liters in 24 hours) This drip may be con tinued for as long as a week or more if necessary and the amount of aminophylline in each liter is gradually reduced as symp toms subside

without oxygen Streptomycin has not been of much value in asthma

The nose and sinuses should be examined in all asthmatic patients Large polyps should be removed and severely deviated nasal septa should be straightened to prevent asthma from pressure on trigger" areas in the nose But the writer is opposed to opera tions on the sinuses unless there is definite infection as shown by pain fever leukocy tosis and a nasal secretion which is high in polymorphonuclear leukocytes and low in eosinophils The era of radical and almost indiscriminate nasal and sinus surgery has ended fortunately for patients

Bronchoscopic aspirations may be lifesav ing especially in patients who are unable to expectorate their thick tenacious sputum. Suffocation may ensue if aspiration is too long delayed The procedure in the hands

of an expert is indicated in all such patients no matter how near death may seem Morphine of course should not be used during the procedure

Sedation in asthmatic patients should be mild e g ½ grain (30 mg) phenobarbital or 1½ grains (0 1 gm) of seconal

It is also necessary to treat all contributory factors as discussed in a preceding page The patient should avoid inhalation of various kinds of dust fumes bacteria and viruses and especially the common "cold" Psychogenic stimuli frequently aggravate asthma and may be checked by suggestion or other means It is more difficult to overcome endocrine influences e g that of oncoming menstruation Wet feet should be avoided also exposure to house cleaning especially

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apy to the chest or spleen and various types of fever treatment e g from intravenous typhoid vaccine or by diathermy may also be of aid in some cases Such agents probably act nonspecifically Foci of infection should be removed

The treatment of complications of asthma will vary with the condition One must care for the asthma and at the same time attack the associated *condition* *Lobectomy* is indicated in asthma with bronchiectasis provided the patient is a good surgical risk and the dilatations have not involved too much lung tissue If an asthmatic patient needs an operation e g herniotomy or cholecystectomy he should first be made asthma free in the hospital (best in an asthma" room) The operation is then performed and the patient returned to the asthma" room to prevent recurrence of asthma which might interfere

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22 asthmatic patients as compared to 6 4 per cent in nonasthmatic persons This percentage of recurrence would be greatly decreased if the patient were kept in an asthma room until the surgical scar is fairly strong

Results of Treatment in Bronchial Asthma Results in paroxysmal asthma are usually brilliant if the above procedures are carried out especially in patients who have had a careful history examination and complete skin tests and laboratory studies All this must be followed by avoidance of offending allergens with hyposensitization when these allergens cannot be completely avoided by the patient

Symptoms in chronic asthma can usually be lessened but complete relief cannot be expected because of such irreversible changes as found in the associated emphysema *

The results are therefore best in children who usually have the paroxysmal type of asthma as shown in Tables III and IV

TABLE III

RESULTS OF TREATMENT IN 459 CASES OF BRONCHIAL ASTHMA

	PAROXYSMAL				CHRONIC			
Age at Onset	*100 per cent Cured*	*Improved*	*Unimproved*	*Dead*	*100 per cent Cured*	*Improved*	*Unimproved*	*Dead*
0 9	55	81	5	3	—	23	9	5
10 19	9	29	6	—	2	13	9	4
20 29	17	27	4	2	—	8	10	4
30 39	8	17	5	1	—	11	7	6
40-49	4	17	—	3	2	7	9	11
50 59		2	1	2	—	9	4	4
60 69			—	—	—	1	—	3
Totals	93	173	21	11	4	72	48	37

* In a recent paper Harvey has presented evidence that the adrenocorticotropic hormone (ACTH) is of value in treating patients with severe intractable asthma The administration of the hormone for 4 to 5 days in a dosage of from 100 to 500 mg daily produced an immediate remission lasting for an indefinite period in some patients In the patients reported cortisone was found not to be nearly so effective as the adrenocorticotropic hormone *Editor*

Harvey A McG The Effects of ACTH and Cortisone in Allergic Diseases (To be published read before the American College of Physicians Boston April 1950)

TABLE IV

SUMMARY OF RESULTS OF THERAPY IN 459 CASES OF BRONCHIAL ASTHMA

	100 per cent ("Cured")	*Improved*	*Unimproved*	*Dead*	*Total*
Paroxysmal	93 (31 2 per cent)	173 (58 0 per cent)	21	11	298
Chronic	4 (2 4 per cent)	72 (44 7 per cent)	48	37	161
Total	97	245	69	48	459

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URTICARIA AND ANGIONEUROTIC EDEMA

Urticaria (hives nettle rash) is an allergic condition characterized by crops of wheals from small to large almost always accompanied by more or less itching The *condition may be acute and be of short* duration It may become chronic and wheals may come and go for many weeks or months even years

Angioneurotic edema (Quincke's disease) is probably due to an allergy The

*in any part of the body but seats of predilec*tion are eyelids tongue lips genitalia and the extremities especially the palms and soles The lesions are almost always unilateral e g the right eye and/or the left foot Older literature to the contrary notwithstanding the swellings rarely affect the throat Patients are sometimes unduly alarmed by the possibility of choking

Etiology as Related to Therapy Urticaria and angioneurotic edema occur at all ages and in both sexes In our experience the hereditary factor is present in only about 25 per cent of cases as compared to about 75 per cent in migraine and 60 per cent in bronchial asthma and hay fever In most patients *therefore these swellings* are not related to a personal or family history of allergy That it can have a hereditary basis

has been shown through five generations by Osler Fairbanks and Crowder and Crowder Migraine and urticaria not infrequently co exist

The cause of attacks is varied In the acute cases certain foods and certain drugs are al most always the exciting factors and it is usually not difficult to track these down and avoid them The foods which are likely to cause these swellings are fresh fruits e g peaches and strawberries fresh vegetables e g tomatoes pork products (any variety) nuts shellfish and perhaps eggs and choco late Milk in a few cases is undoubtedly a cause and milk from one herd of cows may incite hives while that from cows in other parts of the country may not be troublesome It may well be that the antigenic effect of milk depends on the type of food or grazing given the cows It has also been shown that patients are not necessarily sensitive to ber ries or other fruits but rather to something on the outside of these fruits Benson has shown that hives will not occur even in a strawberry sensitive individual if the berries are thoroughly washed in a colander under hot running water Such facts may account for the poor results with skin tests in this type of allergy As a matter of fact the infor mation obtained by skin tests in urticaria and angioneurotic edema is almost always unre liable This writer has therefore discontinued skin testing in this group unless the patient has some other allergic condition Passive transfer tests at this time are useless

Drugs are more likely to lead to angio neurotic edema than are foods especially such drugs as quinine aspirin arsphena [illegible]

less severe urticaria and occasionally angio neurotic edema The rash resembles that of serum sickness in that it often begins from 5 to 10 days after the drug has been used the rash may also begin quickly The lesions may follow injections of these antibiotics or may occur when the drugs are ingested or even after inhalation When a drug is applied as in an ointment any resulting lesion is usually that of a dermatitis at the site of ap plication (contact dermatitis) rather than a generalized urticaria Occasionally however a widespread exfoliative dermatitis may oc cur but this is not usually of an urticarial type

Acute urticaria can also promptly follow an overdosage in hyposensitization (as in the treatment of asthma or hay fever) It can also occur and be troublesome in patients who need and receive insulin liver extract or other endocrine products The role of in halation has not been proved it has been difficult to show that inhalation of house dust can cause hives Inhalation of silk can Acute hives can also occur from such physical agents as cold heat or pressure But in such cases the hives are not as red and itching is frequently absent The lesions themselves are sharply outlined and in this physical al lergy type there is no pseudopodia as occurs in ordinary hives Infection is probably not important in acute hives except as it may lead to the use of a drug

Chronic urticaria and angioneurotic edema are markedly different from the acute types because the condition tends to drag on and to puzzle both the patient and the physician The food factor is certainly less important unless the antigenic food is one which is commonly eaten e g milk Drugs too are less frequent offenders though one must search for such substances as phenobarbital cathartics and ingredients in tooth pastes and mouthwashes In addition coal tar products are commonly used in certain pre pared foods e g the substitution of vanillin for vanilla

It is in this group that infections seem most important especially those in the biliary tract as well as in the teeth tonsils sinuses prostate and pelvic organs Every sufferer with chronic hives should be searched for all these possible foci of infec tion It is especially important to do a roentgen ray of the gallbladder by the Gra ham Cole technic We have been able to clear up obstinate cases by finding and re moving gallstones in patients who denied biliary tract symptoms

Other predisposing factors may also be of some importance e g endocrine and psy choneurotic and efforts along this line may be necessary Urticaria factitia (straight raised red lines due to scratching) is not really urticaria

Treatment Acute Urticaria and Angio neurotic Edema It is necessary first to give

relief and to avoid substances e g more antibiotics which might aggravate the condition *Two types of therapy are available* the new antihistaminic drugs and epinephrine or ephedrine Almost all of the drugs of the first group give good results in these acute cases After trial and error in many cases we have now systematized the treatment as follows In severe cases we try to hospitalize the patients and give (adults) 100 mg of pyribenzamine three times a day with 100 mg of benadryl at night In some cases we also inject about 0 50 cc 1 1000 epinephrine as necessary and may also inject 1 0 cc epinephrine in oil intramuscularly twice a day Antihistaminic drugs can also be inserted under the skin In milder cases 50 mg dosages of an antihistaminic drug may suffice and epinephrine or ephedrine are usually not necessary

It is also advisable to order a saline cathartic to remove as much as possible of the offending food or drug Local applications may be soothing e g calamine lotion or baking soda or cornstarch baths

Avoidance of the cause is *of course* of fundamental importance Sometimes the cause is obvious e g the condition may follow injections of penicillin or ingestion of a drug such as quinine or of such a food as lobster or berries But when the antigen is not evident we advise *elimination diets* The patient is kept away from all medicines and cathartics (except those we give) and from the following foods fresh fruits and vegetables and their juices (frozen foods are considered fresh) peas, beans tomatoes in all forms fish and nuts of all kinds pork including ham bacon lard and some gelatinous compounds chocolate and cocoa, chicle (chewing gum) and cola drinks This diet is successful in many cases If the hives disappear the diet should be maintained for about 2 weeks then one food at a time is added with 4 or 5 days between additions to see if symptoms return If milk is suspected the patient may be put on a strict milk free diet or may be given only milk and cream to see if the urticaria is aggravated Hyposensitization is rarely advised

CHRONIC URTICARIA In this condition the elimination diets and withdrawal of all drugs should also be tried but the results are less successful Infection is important in these chronic sufferers and every effort should be made to discover and to remove any focus of infection especially in the gallbladder Any measure which can allay psychic or endocrine factors may be useful but too much reliance should not be placed on these factors It is doubtful if true urticaria is due solely to a psychic or endocrine maladjustment

Nonspecific measures are numerous and disappointing Pancreatic extracts calcium autohemotherapy ultraviolet light and injections of sodium thiosulfate spleen extracts peptone and vaccines have all been tried with indifferent results Histamine and histaminase (torantil) are given by some workers Dilute hydrochloric acid (30 to 60 minims) with each meal should help those whose gastric acidity is subnormal High protein low sodium acid ash diets have been successful in 6 cases of Rusk and Kenamore potassium chloride was substituted in place of sodium chloride But Vaughan tried this regimen without success

It is highly important that the physician should not give up hope in these cases He should force his patient and himself to continue the search for possible clews Sooner or later the cause can frequently be found It must be admitted however that the lesions may spontaneously disappear, to the *satisfaction of the patient and the bewilderment of the physician*

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SERUM SICKNESS

Serum sickness (*serum* disease or serum

to the serum, not the antitoxin, and may be of the usual delayed type or it may be accelerated or atopic

These reactions have been frequent since the introduction of diphtheria antitoxin in 1890 as especially noted by von Pirquet and Schick in 1905 In recent years reactions have probably been more frequent after tetanus antitoxin than with diphtheria antitoxin With recent refinements in manufacture, delayed reactions are now decidedly less frequent

The three types of serum reactions are as follows

(1) The Usual Delayed Type Fever urticaria adenitis and joint pains frequently occur after the first injection of serum Symptoms usually begin from the 5th to the 11th

especially if given intravenously Age and sex apparently play no part Although horse serum is the usual cause hog and rabbit serum may also cause reactions and reactions occurred in the 17th century after transfusions of lamb's blood Hives may be large or small and profuse or slight The swellings of angioneurotic edema (lips eye lids various other parts of the body) may also occur, and the eruption may also resemble that of measles or scarlet fever, and may come in crops Complications occasionally occur e g neuritis, gastro intestinal hemorrhage abdominal pains purpura jaundice, hematuria atrophy of the liver Menière's syndrome and psychosis Leukopenia and relative lymphocytosis are frequent, but the blood findings are not diagnostic

(2) Accelerated reactions are apt to occur in persons who have previously received serum especially in those who have already had one or more bouts of serum sickness The reactions come on much more quickly, often in a day or two, and occasionally immediately after the injection of the serum The prompt reactions resemble those of anaphylactic shock in the guinea pig, and death may occur Some of these patients have been sensitized by previous injections of serum and others by the now abandoned administration of diphtheria toxin antitoxin (now replaced by the use of diphtheria toxoid) This toxin antitoxin has sensitized from 25 to 27 9 per cent of children

(3) Atopic reactions fortunately are rare as they are apt to be severe and often fatal When antitoxin containing horse serum is injected into a person who is naturally allergic to horse dander, and who has bronchial asthma and/or allergic rhinitis, violent and immediate symptoms of anaphylactic shock may occur The blood pressure falls the white cell count goes down, and acute emphysema and pulmonary edema may follow If death does not occur, asthma, urticaria, rhinitis, and/or angioneurotic edema may be present

It has been shown that there exists an antigenic crossed relationship between sensitivity to horse serum and horse dander Horse dander contains two antigens, the dander antigen and a small amount of the serum antigen An individual allergic to both is apt to have reactions from injections of serums but reactions are unlikely if he is only sensitive to dander In other words not all horse sensitive patients necessarily develop serum sickness if injected with horse serum But the percentage is so high and the danger is so great in such persons that every precaution in giving antitoxin is essential and some physicians simply refuse to use antitoxin in these horse sensitive individuals It is in this group especially, that the prophylactic use of toxoids is imperative, both diphtheria and tetanus toxoids should be given at once to these persons

The treatment of serum sickness is that of prevention and that of the condition after it has occurred The greatest advance lies in the field of prophylaxis

Prevention (Prophylaxis) This involves (1) improvement in serum, (2) care in injecting *antitoxin*, (3) *the use of antitoxins* made from other animals (4) the use of despeciated antitoxins (5) the simultaneous use of epinephrine and/or antihistaminic drugs (6) the role of anesthesia, and, above all, (7) the use of toxoids

(1) Purification and concentration of immune sera have reduced the severity and occurrence of the smaller (delayed) type of serum sickness Whereas about 90 per cent of persons developed urticaria or other symptoms when antitoxin was first introduced, the percentage of reactions has now

Larger doses of 1 1000 epinephrine should be injected at once and repeated as symptoms demand Intravenous or intracardiac administration is rarely necessary, although advisable in an emergency when subcutaneous injections have failed

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CHAPTER XIII

THE ROLE OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND 17-HYDROXY-11-DEHYDROCORTICOSTERONE (CORTISONE) IN PRESENT-DAY THERAPY

Whatever is here written will probably in large measure be outmoded within a short period after publication of this volume In view of the widespread publicity, regarding the effects of ACTH and cortisone in a variety of disease conditions, it is pertinent [illegible] out that neither ACTH nor cortisone represents therapeutic agents Rather, they must be considered to be investigative tools, by means of which disease processes may be studied A consideration of the diverse group of diseases which apparently can be altered by the administration of ACTH or cortisone suggests that the major changes are those induced in the host's response to his disease rather than in the disease process per se

The use of adrenal cortical extract therapeutically is not new Aqueous adrenal cortical extracts and the more potent lipo adrenal cortical extracts have been used as supportive agents for many years, particularly in the treatment of prolonged illnesses severe infectious diseases, and diseases in which alterations of fluid and electrolytes have been of paramount importance Until rather recently the importance of supportive adrenal cortex therapy has been underestimated and not well understood Following early experimental results it was necessary to break down the general action of the adrenal cortex into three groups (1) the electrolyte fluid regulating action, (2) the metabolic regulating action ("S" hormone), and (3) the andro genic action ("N" hormone) Compound A was first studied in the treatment of Addison's disease It was noted that the hypoglycemic attacks which so frequently accompany adequate control with desoxycorticosterone acetate (DCA) were absent when compound A was given with DCA Compounds A and E were later found to have slight effect on the electrolyte abnormalities of Addison's disease when administered alone More recent studies have shown that compounds E and F (11, 17 oxysteroids) are primarily effective in the metabolic regulating action of the adrenal cortex and only mildly effective in the other adrenocortical functions It became apparent then that compound E would have only a secondary role in the treatment of Addison's disease, but might be a necessary factor in the adequate treatment of total and certain types of mixed adrenal cortical insufficiency Further work suggests that there is some antagonistic action between the "S" hormones and DCA as some of the excessive sodium retention due to DCA overdosage may be relieved by the administration of compound E or F

Adrenocorticotropic hormone (ACTH) has also been used experimentally for many years As its name implies, ACTH stimulates the entire adrenal cortex, thereby pro ducing all three general adrenal cortical actions It appears to have little if any thera peutic effect on patients with Addison's dis ease, supporting its role further as a purely adrenal cortical stimulator Until recently, the chief clinical use of ACTH was as a test for the presence of adrenal cortical defi- [illegible] "alarm reaction" of Selye Many investigators feel that both ACTH and cortisone may

be significant factors in both the "alarm reaction" and in the course of the "adaptation diseases" so well described by Selye

At the present time, ACTH and cortisone have been used therapeutically in only a few disease entities, in most of which alterations in mesenchymal tissue seems to be a prominent feature Hench et al have produced rather striking remissions in rheumatoid arthritis rheumatic fever and disseminated lupus erythematosus Thorne et al have had equally good results with ACTH and cortisone in the same diseases and have added gouty arthritis to the growing list Soffer et al claim a remission in one case of myasthenia gravis following ACTH administration The effects of both cortisone and ACTH in such varied conditions as agranulocytosis essential hypertension acute infectious diseases nephrosclerosis anaphylactoid reactions ulcerative colitis and certain mental diseases are under observation at the present time Few conclusions may be drawn, however it is fair to state that both drugs show promise as investigative and therapeutic agents and have produced marked remissions in the few conditions which have been studied and adequately controlled

The recommended dosage for cortisone seems to range initially from 300 mg of the acetate (Merck) to as little as 50 mg daily as a maintenance dose It is usually given intramuscularly in divided doses twice a day ACTH (Armour's standard) has been given in doses ranging from 20 mg to 100 mg. daily divided into four doses The maximal effective action seems to be from 6 to 12 hours after administration The optimal dose must be established individually for each patient under treatment Both drugs produce certain abnormalities when adequate amounts are given thereby aiding the investigator in determining when the optimal therapeutic level has been reached These changes include a marked drop in circulating eosinophils a rise in the circulating neutrophils, a decrease in circulating lymphocytes a rise in the uric acid creatinine ratio in the urine, a rise in circulating and urinary 11 oxysteroids and an increased insulin tolerance These drugs may also produce increased nitrogen excretion in the urine and hyperglycemia ACTH in addition produces an increase in urinary excretion of 17 ketosteroids, initial sodium and chloride retention as evidenced by urinary excretion of these ions, and initially increased potassium excretion Clinically, a Cushing's syndrome and hyperglycemia may become evident. ACTH may also produce a transient hypertension, epigastric distress a sense of exhaustion, and euphoria It has been suggested that some of the side effects of ACTH may actually be due to small amounts of pressor substances from the posterior pituitary present as a contaminant as a result of the manufacturing process

There has been much discussion regarding the dangers of ACTH and cortisone administration It is certainly too early to draw conclusions regarding this matter but at the present time most investigators think that the bad effects are transitory in nature Thorne et al feel that before treatment with cortisone is discontinued, the patient should receive simultaneous decreasing doses of ACTH to offset the decreased endogenous production of the corticosteroids Both ACTH and cortisone may decrease the endogenous production of ACTH and it seems wise to give these patients decreasing doses of ACTH during the withdrawal period

In summary let us reiterate that cortisone and ACTH promise to be of great value in the study of certain disease entities Both drugs act primarily as adrenal corticosteroids ACTH by stimulating release of adrenal corticosteroids, and cortisone by its action as one of the adrenal corticosteroids Both apparently have the ability to alter the host's reaction to certain disease processes Recent investigation with these drugs has stimulated great interest in the further study of the adaptation diseases described by Selye Therapeutically they are of only minor significance at this time owing to the limited production of the drugs and the paucity of knowledge regarding their possible deleterious actions

In the following references, the authors have attempted to list only those papers which have direct bearing on the therapeutic uses of ACTH and cortisone and to articles which are essential to the basic understanding of their mode of action

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DISEASES DUE TO PHYSICAL AGENTS

THERMAL STATES

(1) Sunstroke heat stroke insolation thermic fever hyperthermia siriasis
(2) Heat exhaustion heat shock
(3) *Heat* cramps

These three conditions are entities calling for distinct treatments but all deriving in some degree from disorder of the heat regulating mechanisms

In the first group the characteristic feature is heat retention with highly elevated *body temperature Treatment is to be di*rected primarily to temperature reduction Erstwhile heroic measures of ice packs ice tubbing and ice enemas should give way to prompt air cooling cold sponging and moderately cold packs The higher the temperature elevation the greater the urgency and the warrant for severer chilling No effort should be made to lower the temperature below 101 to 102 ° F Saline or glucose introduction is not indicated Rarely is artificial respiration required Pulmonary edema may appear and necessitate control Rest in the recumbent position should continue for days in more serious instances but with some changes in position This may obviate subsequent unfavorable developments in which convulsive states may arise

In the second group heat dispersion dominates with vasomotor collapse calling for treatment Treatment best suited to mild surgical shock is indicated Intravenous glucose has been both praised and condemned Generally treatment is on the basis of symptomatology

In heat cramps saline depletion notably of muscle tissue with or without accompanying dehydration serves as the basis of the abnormality and determines both therapy and treatment All patients with moderate or severe heat cramps should be given 2 or more liters of physiologic saline solution The intravenous route is superior but the ingestion of 0 5 per cent salt solution may suffice Intake of the usually available 16 grain salt tablets along with water may meet the situation Milk because it contains 0 3 per cent of salt in such quantities as a quart may be superior to an equal concentration of saline Few cases require hospitalization

Despite clinical dissimilarity these three states will respond to the same forms of prevention Protective clothing provides no certainty of escape from insolation The absence of bright sunlight equally guarantees no full safety In indoor activities much may be *gained by scant clothing In general* in *hot* occupations with or without associated high humidity protection to the extent practical should be sought through mechanical dispersion of hot atmospheres

More specifically in hot occupations and for all during excessively hot weather healthy persons may profit by a high intake of salt tablets or by the free drinking of salinized chilled water (0 1 or 0 2 per cent) Increased milk drinking may accomplish the same end If salt tablets are relied on most persons prefer the 0 5 gm content in friable form Some are enteric coated because of the nausea sometimes induced

Once present any one of the three states mentioned tends to recur even at lower exposures For persons facing this prospect extra preventive measures are justified

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MOTION SICKNESS

Sea Sickness, Air Sickness Train Sickness Car Sickness Swing Sickness

These conditions sharing common causation likewise share some degree of responsiveness to the same treatment As a forerunner to statements relative to treatment, it is necessary to mention the four currently accepted bodily sources of such disorders since therapy in some measure may be directed to specific types of motion sickness These are (1) the vestibular apparatus, (2) abnormal visceral motions (3) psychic, (4) combinations of the three The last probably represents the commonest variety

In therapy and prevention scores of different drugs have been utilized with some degree of success for all The number includes atropine compounds, bromides, strychnine, benzedrine, hyoscine and its compounds, hyoscyamine, ergotamine, chlor etone, thiamine, and the barbiturates Various of these substances have been applied in combination At the present time the consensus favors hyoscine or its compounds or in combination with other substances such as acetylsalicylic acid This drug may be introduced orally or in rectal suppositories, in chewing gum, or through tablets for sublingual absorption It may provoke mouth dryness and diminished sweating, mild dizziness, and flushing of the skin These disadvantages when present seldom outweigh the relief frequently provided For prophylactic and therapeutic purposes doses recommended have ranged from 1/400 grain (0 015 mg) to 1/100 grain (0 06 mg) One commercial product represents hyoscine hydrobromide, 1/400 grain, mixed with acetylsalicylic acid, 3 to ½ grains, both incorporated in chewing gum tablets Since gum chewing is a common practice in air flight and somewhat common in sea travel, this approach to therapy is reasonable Another combination for oral intake in tablet form represents 0 1 mg hyoscine camphorate and 0 4 mg hyoscyamine camphorate For suppositories the oral dosage is ordinarily doubled It is good practice to institute motion sickness prevention 1 or 2 hours prior to departure Failure to prevent discomfort in this manner may lead to repeated doses at 3 or 4 hour intervals but therapy at this rate should not extend over more than 24 hours For children over 7, the drug dose is about one half of that for adults, and lower for younger children The aminoxide hydrobromide is said to be superior to the plain hydrobromide

A host of physiologic procedures retards air motion sickness A few are here noted the wearing of dark glasses or otherwise the avoidance of the viewing of apparently moving objects, the wearing of ear defenders for the purpose of some avoidance of noise, sitting or lying in the line of motion rather than sideways, the avoidance of excessive alcohol or food intake, although light food intake may be favored *

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* Recently Gay and Carliner have described a new drug b-dimethyaminoethyl benzhydryl ether 8 chlorotheophyllinate as being effective in seasickness and motion sickness This drug marketed under the trade name of dramamine received extensive trial by the Army during the last war and was successful in preventing the distressing symptoms of seasickness The dosage is 100 mg before each meal and at bedtime It now appears to be the drug of choice in all types of motion sickness — *Editor*

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MOUNTAIN SICKNESS

(Air Sickness)

Man's diseases, and correspondingly treatment therefor, at high altitudes distinctly are influenced by his rate of *ascent, energy* expenditures in the process, and the total elapsed time (acclimatization) involved Manifestly, rapid decompression and fast *motion* characteristic of other forms of "air sickness," *do not occur in "mountain sickness"* Oxygen intake *so essential both for* prophylaxis and cure for anoxia in connection with high altitude aviation, is far less serviceable or usable in mountain sickness The prime therapy of mountain sickness is on the physiologic level and centers about acclimatization, with a different acclimation requirement for every significant increase in *elevation Without medical* influence, the body *adapts itself through readjustments to* modified tensions of carbon dioxide, oxygen and to altered respiratory rate and excursion The number of red blood cells significantly increases and physical exercise becomes increasingly burdensome Alkalosis makes its appearance

For the sick and the frail, medical care may be required at even the 5000 ft level *Scant exercise is in order Intermittent* oxygen *intake may be provided, although this* procedure may interfere with physiologic readjustments Mental and emotional states may suggest mild sedation, but psychotherapy may be more commendable At the 14000 ft level the highest reached by any large number of individuals in this country (Pike's Peak) a fair percentage of visitors *presents genuine mountain sickness in which* panic or at least fright is a frequent feature Obviously this means that physicians throughout the country are consulted by those planning any such excursions into the higher regions His advices for the unadjusted should emphasize minimal exertion, if practical periods of inurement at lower *level, the avoidance of panic, recognition of* prospects of impaired judgment, and pos*sibly trivial* sedation Clearly certain physical states such as pronounced emphysema, should preclude or deter any such ascents The return of the acclimated person to levels below 1000 ft may be accompanied by somewhat similar discomfiture which *again resolves* on the basis of physiologic adjustment with *time as a factor*

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DECOMPRESSION DISEASE

Caisson disease has emerged from the aquasphere and in reverse fashion has entered the stratosphere This classical term *should give way* to or be associated with *others such as "aero embolism" "compres*sion disease," 'decompression disease," "bends," etc Wherever encountered, the condition derives from the formation of ni trogen bubbles in the tissues or joint spaces wholly unexpected in man's normal gaseou balance at the earth's surface In strato spheric occurrence, anoxia, low tempera *tures, and occasionally gravitational abnor malities confuse but do not directly* ente the situation

All treatment is prophylactic or physical The fundamental requirement is to preven the formation of the nitrogen bubbles or t get rid of them High altitude (above 3000 ft, 226 mm Hg) flying requires for pilot pre periods of moderate *exercise with* in *creased intake of oxygen to reduce nitrogena* tion of tissues together with gaseous elimina tion from the intestinal tract, etc Fo passengers, pressurized aircraft is requisit to flight beyond readily predetermined a titudes Descent to lower levels may ame iorate symptoms, but reascent accentuate *manifestations, apparently from expansion* *nitrogen bubbles not fully dispersed* Ind vidual susceptibility is pronounced

In underwater work in which hard lab may be performed under several multipl of normal atmospheric pressure and for rel tively prolonged periods, caisson disease bends is inevitable unless *slow, regulate somewhat standardized decompression* is i stituted in ascent Failure to obviate tl

disease requires prompt recompression in surface chambers designed for that purpose or otherwise actual resubmersion Oxygen *intake in surface chambers is desirable* Artificial atmospheres with helium substituted for nitrogen promises to diminish the perils of caisson exposure, since helium disperses much more readily than nitrogen At times *treatment with inhalators furnishing 20 per* cent oxygen and 80 per cent helium may prove more satisfactory than pure oxygen

of a visible water line through the tympanum or other significant signs may be expected to recover without specific treatment within 6 weeks provided further exposure insult is avoided

Aerodentalgia a common feature of air travel and presumably chiefly due to expanding gas bubbles may justify the use of analgesics Comfort usually is restored on landing Otherwise or if repeatedly disturbing in flights dental care should be obtained

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ELECTRIC SHOCK

Electric injuries occur with such wide variation in site and severity that suitable therapy may not be anticipated for every situation In general requirements of treatment fall into three categories (1) emergency care immediately following the rescue of the victim (2) surgical care of external injuries usually burns (3) care of early or late sequelae should any appear Opportunities for sequelae are legion These may range from slowly developing cataracts to traumatic neuroses

In this publication consideration may be directed only to the first item Assuming that the electrically shocked individual has been *removed from further exposure* and has not suffered other injuries for example from falls three items require appraisal (1) The patient may be unconscious and not breathing Manual artificial respiration should be *administered promptly*, with preference at this time for the Schaefer method Resistance to the resumption of breathing by a viable person may be great The use of oxygen or oxygen dioxide mixtures is indicated Mechanical artificial respiration is to be con

doned only if conducted by skilled operators In the absence of restored breathing some form of artificial respiration should be continued until rigor mortis indicates defeat (2) During artificial respiration or in its absence if unnecessary, surgical shock may be present or imminent The same therapeutic procedures that apply to any surgical shock are suitable here and the same urgency exists (3) A common major critical threat in electrical shock is ventricular fibrillation It is thought by some that ventricular fibrillation in electric shock may not be quite so fulminating as ventricular fibrillation in *some other states Even so there is scarcely* opportunity for therapy Under laboratory conditions countershocking through the chest wall with currents at 30 ampere levels may *be efficacious* The introduction of 2 cc of potassium chloride (0 5 per cent) into the arterial system followed by a solution of 10 cc of calcium chloride (0 023 gm) may likewise control ventricular fibrillation Obviously neither procedure is practical for the electric shock emergency Johnstone has suggested that acetyl methylcholine chloride in small doses might be considered for the control of fibrillation It appears unlikely that epinephrine serves other than harmful purposes in this cardiac state

[illegible]

should be kept in bed for 1 to 2 weeks Judicious treatment during this period may ward off latent effects either emotional or organic

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CARBON MONOXIDE ASPHYXIA

The single action of carbon monoxide is on the hemoglobin robbing that tissue of *its oxygen carrying* power Consequently, the essence of treatment centers about the removal of carbon monoxide from its association with hemoglobin In less severe cases, carbon monoxide, obeying the laws of gases rapidly dissociates spontaneously but even these milder involvements should not be accompanied by any unnecessary expenditure of the patient s energy Effort exaggerates symptoms In more severe instances after removal from further exposure the patient *should be subjected to the best available* means for promoting pulmonary ventilation Only infrequently does respiration cease in a viable person but artificial respiration may *be required It is always possible to institute* manual artificial respiration employing the method of choice of the physician If at all available and as rapidly as possible the inhalation of oxygen should be instituted either in connection with the patients breathing or with artificial respiration if required Mechanical artificial respiration is fraught with some dangers notably if conducted by poorly trained laymen The mask of the oxygen inhalator should not be strapped over the face since undetected vomiting may lead to drowning Except in the mildest of carbon monoxide asphyxia oxygen inhalation if available is beneficial and should be employed even though the patient appears to be in good condition since its use frequently and promptly eliminates disturbing manifestations such as headaches Superior to oxygen alone is oxygen mixed with carbon dioxide at the 5 7 or 10 per cent level of the latter Availability commonly determines the percentage Carbon dioxide serves as a respiratory stimulant and promotes pulmonary ventilation Coma ordinarily appears when the blood saturation with carbon monoxide is near 40 per cent above 60 per cent death is imminent Within the zone of 40 to 60 per cent the prompt utilization of oxygen carbon dioxide mixtures readily may reduce the saturation percentage by 50 per cent within 30 minutes or 1 hour During this early period the patient [illegible] some [illegible] nds within the chest During this stage it is commonly true that some dilatation of the heart exists therefore the patient should be kept quiet and warm The intake of oxygen or

oxygen-carbon dioxide mixtures should be continued for longer periods represented by hours but tapering off with intermittency If blood samples have been collected (usually after reaching the hospital) these eventually indicate minor percentile saturation It may not be necessary to continue oxygen inhalation solely for the purpose of eliminating these residual traces The usual tobacco smoker may yield evidence of 2 to 4 per cent of blood saturation and without symptoms or known significance After the period of emergency treatment the patient without physical effort on his own part should be hospitalized as symptoms tend to recur calling for further inhalation therapy Resort to drugs is usually futile Guarded exception may be made in favor of 7½ grains (0 5 gm) of caffeine sodium benzoate and coramine (pyridine β carboxylic acid diethylamide) 1 cc intravenously Drug introduction subcutaneously is less effective because of the impaired circulation

While chronic carbon monoxide poisoning is a misconception chronic exposure is well established So called "chronic poisoning" customarily represents repeated acute episodes or the sequelae of gross acute poisoning Sequelae on an organic basis are not to be expected unless the acute stage has been severe as reflected by coma or near coma extending into 3 or 5 hours duration The nature and site of organic sequelae are unpredictable but all stem from anoxia Any organ or tissue may be involved The range may extend from minor persistent headaches to optic atrophy psychopathic states or gangrene of a member Manifestly treatment of sequelae be they early or late must be adapted to the individual situation

Carbon monoxide victims are peculiarly prone to subsequent psychoneurotic states From the beginning the physician ministering to a conscious patient both negatively and positively should seek to fend off provocation to neuroses Apart from the requirements of the early emergency situation possibly the most difficult of therapeutic tasks on the part of the physician is to protect the carbon monoxide victim against functional disorders When neuroses arise therapy in nowise departs from that suitable to such disorders from any other source

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ATOMIC RADIATION INJURIES

The
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grosser secondary effects resulting in changes in the various organ systems of men and animals have been observed for a period long enough to permit an approach to the treatment of injuries produced by ionizing radiations

The radiations released in nuclear fission cover the entire spectrum of radiant energy from gamma rays through infra red They include neutrons protons alpha particles electrons and the radioactive products of fission of plutonium or uranium in the case of an atomic bomb explosion as well as plutonium or uranium which has not undergone fission These radiations and radioactive elements may affect the body by irradiation of the surface or following ingestion or inhalation of particulate radioactive materials by irradiation of the internal environment

The effects of these radiations manifest themselves clinically for the greatest part in changes in the hematopoietic system the digestive tract skin and gonads Roughly stated the clinical course following radiation injury depends on primary cellular injury and secondarily from continued injury from absorption of toxic substances of an ill defined nature and bacterial infection

Studies conducted on survivors of the Hiroshima and Nagasaki exposures would seem to indicate that all persons exposed to 100 roentgens of total body radiation or less will survive Those exposed to from 100 to 300 roentgens will be seriously damaged but may live if properly and vigorously treated whereas those subjected to more than 300 roentgens will almost certainly die in spite of detailed application of known therapeutic measures

The extent and nature of the injury sustained are dependent on certain factors These include the total quantity of radiation

to which the body is exposed, part of the body exposed, the types of radioactive particles affecting the body, and the energy of the particles and radiations As an example, the neutron has a "biologic effectiveness" or capacity for damaging tissue from 10 to 20 times that of gamma radiation, whereas very "long" or "soft" secondary roentgen rays have a destructive capacity of roughly 1/20th that of gamma rays

The treatment of casualties of an atomic bomb explosion is complicated by the multiplicity of the nature of the bodily damage In addition to the acute and late radiation effects, there are those of solid blast, thermal, infra red, and ultraviolet burns, and trauma from falling structures The treatment of these depends, of course on well established principles of traumatic surgery and medicine These include the alleviation of the shocklike state induced by the aforementioned factors Recent studies indicate the importance of the rapid elimination of inhaled or ingested radioactive substances from the body A means for accomplishing the partial elimination of plutonium and radioyttrium in experimental animals has been devised The treatment of an acute shocklike state is that of traumatic shock from any cause early and generous administration of plasma plus adequate sedation Definitive treatment of burns with sterile pressure dressings and débridement of traumatic wounds is of utmost importance because of the subsequent interference with immune mechanisms The surface of the body and wounds themselves must be decontaminated from radioactive materials by appropriate means if they are found to be present

Damage to the epithelium of the entire gastro-intestinal tract leads, on the second to seventh day after severe radiation exposure, to marked loss of electrolytes and body fluids Close attention should be given to the restoration of fluid and electrolyte balance Leukopenia appears rapidly after radiation damage A disappearance of circulating lymphocytes is promptly seen followed in a day by a loss of granulocytes, depending in its degree on the severity of radiation exposure Within a few days following the appearance of this leukopenia, clinical manifestations are seen similar to those present in an acute agranulocytic angina, involving the pharynx, tonsils, and mucosae of the mouth and nose Vigorous and prolonged use of the antibiotics, penicillin and streptomycin, parenterally and the sulfonamides if renal function permits, is a necessity until the immune mechanisms, including a return of the white blood count to normal, are re-established

Following radiation damage of moderate to severe degree, purpura and other hemorrhagic manifestations may appear from the fourth to 14th day A marked decrease in the number of platelets in the peripheral blood occurs Concomitant with this a progressive increase in a circulating "heparin like" protamine titratable substance appears which inhibits the clotting mechanism Moreover, eventually a rapidly progressive anemia, dependent on both blood loss and failure of the erythropoietic mechanism, appears

Repeated transfusions of whole blood in [illegible]

require approximately 25 liters of blood administered during the first several weeks after exposure and that the administration of blood will, on the average, be prolonged for as long as 8 to 12 weeks Transfusions should begin before a decided fall in the red blood count is apparent

The parenteral administration of protamine sulfate and toluidine blue has been effective in combating the hemorrhagic manifestations in dogs accompanying the appearance of the circulating heparin like substance A suggested regimen for the administration of these drugs in man is the use of 6 to 8 mg of toluidine blue per kilogram of body weight dissolved in a physiologic solution of saline and administered intravenously over a period of 2 hours daily for 3 days, followed by half this dose on subsequent days Protamine sulfate may be given intravenously in dosage of 150 mg in saline solution over an hour's period, accompanied by 50 mg in 5 ml aqueous solution intramuscularly This is followed by the same dosage intramuscularly every 4 to 6 hours until the protamine titration returns to a normal level of 0 140 mg of protamine

In general practice it is extremely difficult to determine the presence of plutonium or

other radioactive substances within the body except by elaborate physicochemical pro cedures However, assuming that this is prac ticable and that plutonium or radioyttrium is demonstrated in the body or is known to have been incorporated into the body parenterally or through the digestive or respiratory tract then it is important that these substances be eliminated as rapidly as possible By continued irradiation of the site of their deposition these substances induce late neoplastic changes

It has been shown that the intravenous administration of zirconium citrate results in [illegible]

mental animal have shown that following a long latent period of many months to years plutonium stored in the bone results in the production of osteogenic sarcomas Animal experiments indicate that the therapeutic use of zirconium citrate may be a valuable addition to the armamentarium available in the treatment of persons exposed to pluto nium and radioyttrium The present state of development in this field does not as yet permit of definitive dosage schedules for the human

In summary the therapy of radiation in juries includes the vigorous primary treat ment of the acute shocklike state mainte nance of fluid and electrolyte balance decontamination of the body s surfaces of both bacterial and radioactive contaminants prolonged administration of antibiotics early and adequate use of whole blood transfu sions and the administration of protamine sulfate and toluidine blue for the control of [illegible]

intravenously in known cases of plutonium or radioyttrium poisoning may be of great importance

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CHAPTER XV

DISEASES DUE TO INTOXICATIONS

ACUTE ALCOHOLISM

Symptoms of acute alcoholism have been correlated in recent years with blood alcohol concentrations and there is good evidence that the values obtained from the blood are identical with the concentration in the brain The rapidly established equilibrium between the blood alcohol and the alveolar air permits the use of expired air for alcohol determinations (Ellerbrook and Van Gaasbeek, Muehlberger) Usually blood concentrations of 0 05 per cent (0 5 mg per cubic centimeter) are considered harmless Three times this concentration is already harmful and is considered as evidence of intoxication, with 0 25 per cent gross lack of co ordination is obvious, 0 4 per cent produces deep and possibly fatal coma The increased tolerance of the habitual drinker is not completely understood, but probably is based on tissue tolerance and psychic factors rather than on a difference in the ability of the body to handle the alcohol

Alcohol is rapidly absorbed even from the stomach and the average person can oxidize about ¼ oz per hour if moderate amounts have been taken, thus 4 oz of whiskey or 10 times as much beer will be eliminated in 5 to 6 hours The congeners of ethyl alcohol, the so called "fusel" oils which are present in poorer grades of liquors (up to 0 5 per cent), [illegible] the oxidation of ethyl alco [illegible] increase of its [illegible] Jellinek, Haggard et al)

The physician will be called on to treat acute alcoholic poisoning only in severe cases Many forms of treatment have been recommended and it is impossible to discuss all of them In the following, a number of procedures are described which should be useful not only for the various forms of alcoholic intoxication, but also to give the physician an opportunity to select the method most suitable to the individual circumstances under which he has to attend his patient

The acute alcoholic attack of the occasional heavy drinker or a sudden exacerbation of the chronic alcoholic in uncomplicated form will frequently confront the physician with a boisterous, hard to manage patient In the absence of manifestations indicating impending delirium tremens or of evidence of organic illness, particularly of the heart, or severe malnutrition we have seen prompt success from the subcutaneous administration of 1/10 grain (6 mg), of apomorphine hydrochloride This is followed within a few minutes by nausea vomiting and a marked sedative effect Frequently this procedure will be enough to sober the patient up and bring him out of the acute phase In cases where this treatment is not necessary or is inadvisable, vomiting should be induced by mechanical means, if possible Sedation is frequently required and should be induced by paraldehyde, by mouth mixed in cold fluid, or rectally in a thin starch suspension

The initial dose has to be varied according to the individual patient and lies usually between 8 and 20 cc This can be followed by additional doses of 8 cc at 1 or 2 hour intervals, if needed Paraldehyde can be injected intramuscularly in doses of 10 cc, intravenous administration should preferably be avoided (Chapman) While paraldehyde is preferred by most authors barbiturates may be useful Morphine should be avoided in this condition The patient should be encouraged to take fluids as soon as possible particularly fruit juices and sugar Thiamine hydrochloride can be admini tered in doses of 25 to 50 mg by mouth o by injection The judicious use of amphe amine 10 mg, mornings and at noon hel sometimes to shorten the subjective sym toms of the hangover period (Mille Analgesics may be administered and a b biturate given for the night because sleep an important factor for recovery

Acute alcoholic psychosis characterized by temporary complete disorientation impending or fully developed delirium tremens with hallucinations requires frequently a more prolonged treatment The long disputed theory that delirium tremens is due to sudden withdrawal of alcohol has been abandoned Today many physicians favor abrupt withdrawal of alcohol but others still believe in a more gradual procedure

Most of the modern schemes of treatment are built around ample administration of fluids and carbohydrates first intravenously if necessary and later orally and the injection of insulin either in relatively small doses or in larger ones with the intent of producing defin te hypoglycemia

While there are experimental data demonstrating that insulin hastens the oxidation of alcohol in animals and man these claims have been disputed by some investigators The majority of clinical investigators believe such procedures to be of definite value

A treatment scheme which is relatively simple to conduct and which provides for a gradual withdrawal of alcohol begins with the intravenous injection of 50 cc of 50 per cent dextrose together with 10 units of insulin and 1 cc of an injectable vitamin B complex solution (Nason) This procedure may be repeated up to five times at 4 hour intervals if necessary After the acute phase has passed the patient is given 2 oz of whisky diluted with 6 oz of water This is repeated at 3 hour intervals for five doses Three more such drinks are suggested but [illegible] e the [illegible] tened [illegible] isume salted foods because the blood chlorides are frequently lowered in this condition Usually the patient should be mentally clear in 30 to 33 hours except in severe cases which require prolonged treatment in the hospital

A somewhat different procedure does not provide for any alcohol administration but uses h gher doses of insulin to cause definite hypoglycemia and accord ngly requires careful medical supervision (Robinson) The pat ent is given 20 units of insulin subcutaneously on admission and encouraged to take 30 oz of orange juice during the next 3 hours This is followed by a second injection of 20 units of insulin Usually the first dose causes hunger and ample carbohydrates are given Most patients quiet down and fall asleep within an hour or two after the second injection Otherwise a third dose of insulin may be given 3 hours after the last one with carbohydrates by mouth or if necessary 500 cc of 10 per cent dextrose by intravenous infusion This treatment may be repeated as a whole or in part if the patient is not clear within 5 hours after he awakens from his sleep Usually recovery occurs in 36 hours Insulin shock should be prevented and will not occur if the patient is watched and carbohydrates are taken in adequate amounts

These procedures can be supplemented by sedation with paraldehyde or barbiturates if required and administration of thiamine hydrochloride Amphetamine desoxyephedrine or dexedrine can be used to combat mental depression as mentioned above

Tepid baths are also recommended as helpful in quieting excited patients

In the severest cases of acute alcohol intoxication the patient will be found in profound coma and energetic methods will have to be instituted It should be remembered that alcohol is not infrequently used as a carrier for other poisons as for instance barbiturates or the patient may also suffer from an endogenous condition Blood alcohol determination will be helpful in such cases

[illegible]

should include inhalation with carbon dioxide because this gas has been shown experimentally to increase the tolerance to otherwise fatal concentrations of alcohol Analeptic drugs as metrazol nikethamide (coramine) or picrotoxin are of symptomatic value The last named drug needs some skill for safe and effective administration (see under Barbiturate Poisoning) (Moore) Intravenous (10 to 15 mg) and later intramuscular injections (15 to 30 mg) or desoxyephedrine (desoxyn methedine) at intervals of 1 hour can be tried Blood pressure and heart action should be watched especially in older persons *

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* Recently adm nistration of mepl enesin (known under the trade names myanes n tolserol or Is sephen) has been suggested on tl e basis of work

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POISONING WITH METHYL ALCOHOL (METHANOL)

This dangerous substance, also called wood alcohol is frequently used for industrial and other purposes and poisoning has occurred with materials which do not immediately suggest the presence of methyl alcohol Inhalation of the vapor is likewise dangerous The acute fatal dose of methyl alcohol in animals is greater than with ethyl alcohol, but the over all toxicity of methyl alcohol is much greater One reason for this is its extremely slow oxidation, a single large dose may take a week for detoxification Formaldehyde and formic acid are assumed to be two of its oxidation products and it is believed by many writers that these highly toxic chemicals are at least partly responsible for some of the toxic effect, as, for instance the well known impairment of vision Increased formic acid excretion in the urine has been shown to occur in severe methyl alcohol poisoning (Lund) Individual susceptibility to methyl alcohol varies greatly, and while usually 100 to 150 cc are considered fatal for an adult doses as low as 30 cc have occasionally been reported to have resulted in fatalities The same variation exists regarding the damage to the eyes but in some persons permanent blindness has resulted from as little as 10 cc The early symptoms of methanol poisoning may be mistaken as being caused by ethyl alcohol However, certain symptoms, as marked abdominal pain, weakness and visual disturbances, dyspnea with marked cyanosis and lowering of blood pressure are suspicious signs Death may occur quickly, or the patient may linger on for a few days. The death rate is much higher than with ethyl alcohol The fatal blood concentration for methyl alcohol is similar to that of ethyl alcohol namely, about 0 5 per cent Treatment should be vigorous and carefully supervised One of the main objectives is to combat the marked acidosis which develops quickly (Chew et al) The stomach should be emptied and a saline laxative administered, if necessary by stomach tube This is followed by 6 gm of sodium bicarbonate orally Four 40 cc ampules of sodium r lactate molar solution are added to a liter of isotonic Ringer solution and administered by intravenous drip If sodium r lactate is not available, a 5 per cent solution of sodium bicarbonate freshly prepared by dissolving 1.25 gm. of sodium bicarbonate in 250 cc. of sterile Ringer solution (do not autoclave) can be

by Schlann and Unna Doses of 0 5 to 1 gm four times daily are said to be useful in promoting sedation and relaxation as well as decreasing anxiety and tremor This treatment may be used supplementing other procedures and may reduce the amount of barbiturates used in some of them While some authors have already given as much as 3 gm of this drug every 4 hours for 2 days or even administered it intravenously, it is advisable to await further confirmation of the usefulness and safety of this regimen before it can replace proved schemes

Both the anterior pituitary adrenocorticotropic hormone (ACTH) and adrenocortical extract (ACE) have been recently studied in the treatment of Korsakoff's psychosis, acute alcoholic intoxication and delirium tremens Both hormones seem to be about equally effective in the treatment of acute alcoholic intoxication ACE having a greater sedative effect and ACTH affecting anorexia more rapidly ACE was given some preference in this condition because of its greater sedative action On the other hand ACTH was more effective in the treatment of delirium tremens than ACE These are initial results which demand further verification and experience —*Editor*

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given instead The effect on the alkali re serve is tested by determining plasma car bon dioxide combining power before and after the administration of this solution If facilities for this are not available the urin ary pH may be used as a guide This treat ment is continued by intravenous infusion and by oral doses of 2 gm of sodium bicar bonate at 1 or 2 hour intervals until the car bon dioxide combining power is normal or the urinary pH has reached approximately the value of 7 Sodium bicarbonate should be discontinued after the urinary pH has reached 7 8 This may take several days Similar therapeutic schemes suggest starting with 1000 cc of 5 per cent dextrose solution in which 15 gm of sodium bicarbonate have been dissolved This solution is infused in travenously for 1 hour and repeated every 6 hours Oral sodium bicarbonate 6 gm every 2 hours is given until the urinary pH is 7 0 which is then maintained at this level (Jacob son) Further supportive treatment consists of administration of vitamin B complex and carbohydrate rich foods The acute stage may require lowering of the intracranial pressure by spinal puncture if indicated and the injections of stimulants in case of severe collapse Administration of ethyl alcohol has been recommended on the basis of theoreti cal considerations by Scandinavian authors but actual clinical evidence for this treat ment is lacking

Higher Alcohols As a rule the acute toxicity of these alcohols increases with the molecular weight Of greatest practical im portance is the isopropyl alcohol which is also used as rubbing alcohol Small amounts as for instance 20 cc diluted with water have caused no significant effects Larger doses lead to a state of alcoholic intoxication similar to severe ethyl alcohol poisoning with coma sometimes accompanied with convulsive manifestations Isopropyl alcohol is partially oxidized to acetone Treatment is symptomatic and should include intravenous glucose saline or lactate Ringer solutions in severe cases

n Butyl alcohol in a mixture with esters has been reported to have caused damage to the cornea and liver

Iso amyl alcohol is the main constituent of the so-called "fusel oils" It is more toxic than ethyl alcohol but as described above the small amounts contained in cheap liquors do not significantly affect their toxicity Treatment is symptomatic and should take in account the slower oxidation of many of these alcohols as compared with ethyl alcohol

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BARBITURATE POISONING

The incidence of barbiturate poisoning has increased continuously with the popularity of these drugs with the medical profession and the public In a review of poisonings which the author made for the years 1938 1939 on the basis of the records of the Cook County Hospital in Chicago the barbitu rates occupied second place in frequency and were surpassed only by alcohol The mortality was 6 5 per cent According to the Metropolitan Life Insurance Company 5 5 per cent of fatal accidental poisonings were due to barbiturates in the early 1930 s

ity that barbiturate intoxication may be the sole or contributory cause of coma if a patient is found under suspicious circum stances The combined ingestion of barbi turates with other drugs especially alcohol or opiates may complicate the issue both from a diagnostic and therapeutic viewpoint Since legal questions are frequently involved the physician will do well to make a careful survey of the circumstances under which the patient has been found look for empty con tainers and preserve if possible the contents

of glasses as well as stomach washings and urine These containers should be properly sealed marked for identification and sent to a competent toxicologist at once Modern chemical methods of detection will enable an expert to give the attending physician a quick reply regarding the presence of barbiturates However a negative test does not necessarily exclude the possibility of a barbiturate poisoning

Our discussion will be concerned only with the treatment of subacute barbiturate poisoning which follows the accidental or much more frequently suicidal overdosage with these drugs We will not consider the management of acute respiratory depression as it may occur during intravenous barbiturate administration

The question of the so called minimal lethal dose of the various barbiturate derivatives has been repeatedly discussed but in the light of his experience and a critical survey of the literature it appears to the writer that the determination of such a dose is almost impossible and certainly of little value for the physician who wants to assess the prognosis of an individual case *This is* especially true since frequently the amount taken is not known The often quoted statement that death will usually occur if 15 or more times the average therapeutic dose of a particular barbiturate has been taken can still be used as a rough guide But this assumption *has to be greatly modified* according to the circumstances Unfavorable influences are old age obesity organic diseases and a long interval between the ingestion of the drug and the institution of proper treatment combined poisoning with other depressant drugs especially opiates or *large doses of* alcohol are likewise aggravating factors

The onset of symptoms and the rapidity of their progress depend on numerous factors such as the dose and type of drug used whether it is taken alone or with alcohol and the amount of food present in the digestive tract In the great majority of cases the effects usually begin after half an hour and are followed by a gradually increasing depression which leads to deep coma with complete areflexia *impaired respiration* and sometimes to death due to general depression pulmonary complications or cerebral edema after 3 or more days Pulmonary *complications may still be fatal* after the patient is already recovering from the barbiturate coma In rare cases however fatal depression may occur within an hour as the result of respiratory paralysis especially if large doses of the fast acting barbiturates as sodium salts (the commonly marketed form) are *taken Under such circumstances* the diagnosis will usually be made too late for effective treatment

Numerous therapeutic measures and antidotes have been recommended for the management of subacute barbiturate poisoning It should be stated that patients who have *taken only a slight overdose of barbiturates* and are found in a condition of mild depression will commonly recover with some supportive treatment without the need for rigorous measures if they show good color normal blood pressure and respiration and react to stimuli It must be emphasized however that even such patients need close supervision in order to detect any deepening of the coma which may occur owing to absorption of the drug still present in the intestinal tract *For this* reason a stomach lavage either with plain water or a 1 5000 solution of potassium permanganate should be performed on all patients with care to avoid aspiration Emetics either orally or parenterally should not be given to the depressed individual After the gastric lavage *a laxative dose of sodium sulfate or sodium* phosphate should be left in the stomach to hasten elimination Severe cases of barbiturate poisoning which are characterized by depressed slowed respiration (*frequently* accompanied by gurgling sounds due to accumulated mucus) cyanosis cold clammy skin and low blood pressure need careful attention A quick check of the reflexes is helpful in determining the depth of coma This may be considered severe if there is no *response to painful stimuli if the* corneal reflex or the response of the pupil to light is absent or sluggish While we cannot discuss diagnostic methods in detail in our own experience we are in agreement with *Alexander* that the intravenous injection of metrazol in 10 per cent solution is a good procedure to gauge the degree of depression The first injection is usually 1 or 2 cc given quickly and if no response is elicited 3 to 4

cc are given a few minutes later Metrazol will exert a brief but powerful stimulation of the respiration in patients depressed by barbiturates and the degree or absence of the response is a rough measure of the pro foundness of the depression This procedure is also of some differential diagnostic value Heinrich has found that 2 to 3 cc of met razol will cause simulation of some degree in coma due to endogenous causes or carbon *monoxide poisoning Absence of such an* effect from this dose or from 3 to 5 cc of metrazol is supportive evidence of deep bar biturate depression

The first measures to be taken in all cases

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cleared by suction using a soft rubber cathe ter, at half an hour or hourly intervals as needed We have found the administration of atropine sulfate in doses of 1/160 to 1/100 gram (0 4 to 0 6 mg) repeated as needed, to be useful in reducing excessive secretion An airway should be inserted to prevent the tongue from falling back and interfering with respiration Oral hygiene will help to reduce damage and infection of the mucous mem branes of mouth and throat Oxygen admin istration is imperative in all cases of severe and prolonged barbiturate poisoning and is usually best accomplished by proper inser tion of a nasal catheter which must be frequently removed and cleaned This is continued until all danger of hypoxia is definitely eliminated In some cases the help of a skilled anesthetist or bronchoscopist may become indispensable to prevent pulmonary atelactasis and to perform endotracheal intubation We have found it advantageous to raise the foot of the bed slightly, espe cially in patients in whom the gag and swal lowing reflex is absent, aspiration of mucus is a frequent cause of dangerous and some times fatal bronchial infections or even pul monary abscesses The patient should be *frequently turned from one side to the other* to prevent, as far as possible hypostatic congestion of the lungs

After these measures have been taken the appearance of many patients will be greatly improved, the depressed blood pressure will rise again the rales will disappear, and normal color will return In others, however, improvement will be only slight and it is our opinion that further benefit can be ob tained by vigorous antidotal treatment with stimulant drugs

The danger of prolonged deep depression in any patient is obvious and is the result of multiple factors, among which poor respira tory movements muscular atonia with pool ing of blood and the possibility of aspiration

these factors Its primary aim must not be to awaken the patient as quickly as possible, but to restore normal reflex activity and improve respiration muscle tone, and cir culation While many stimulants such as strychnine, caffeine and nikethamide (cora mine) are of benefit in producing some *stimulating effect in moderate depression* the best available experimental and clinical evidence points to picrotoxin as the most powerful and useful antidote in severe bar biturate poisoning This nonalkaloidal drug, which has an exquisite antagonistic effect on the central nervous system against bar biturates has been introduced into the treat ment of this condition on the basis of the work done by Maloney, Fitch and Tatum Its efficacy has been endorsed by numerous investigators who have extensive experiences with its use This fact is by now established far beyond the rather conservative evalua tion which was made by the Council of Pharmacy and Chemistry of the A M A in 1939 Pentamethylenetetrazol (metrazol) can probably be considered the second drug in order of potency and is quite useful under certain circumstances as will be discussed shortly In contrast to the above named, such drugs as amphetamine (benzedrine) and desoxyephedrine (desoxyn, methedrine) pos sess not only a central stimulating effect but also influence the circulation directly by their sympathomimetic stimulating action Their usefulness in severe barbiturate poison ing appears promising but is not yet as fully established as that of the other two drugs This subject has been reviewed re-

Picrotoxin is indicated only in severe cases of barbiturate poisoning and the hospital

should have a supply on hand sufficient to conduct vigorous treatment If a patient is in deep coma with negative reflexes and absence of pain responses picrotoxin should be administered intravenously after the above described measures for adequate oxygenation etc have been carried out It is most convenient to inject the drug into the tubing of an intravenous drip infusion The first dose should be 2 to 4 cc of a 0 3 per cent picrotoxin solution The response of the patient should be watched during the next 15 minutes The physician must never forget that picrotoxin even by intravenous administration has a latent period and a prolonged effect The first positive action may consist of a slight and perhaps only transitory improvement of respiration or return of the corneal or pupillary reflex If such response is absent or only fleeting another dose is injected 15 minutes later Under most careful supervision this procedure is continued and the single doses may be raised to 5 or 6 cc Stimulation is thus cautiously continued until the gag reflex returns the respiration improves and the patient responds to painful stimuli or makes spontaneous movements It is most important to watch for signs of over stimulation as evidenced by slight twitching of the facial muscles or of the extremities Attempts to arouse the patient by the continuation of large doses of picrotoxin will almost certainly lead to generalized convulsions A short transitory convulsive attack lasts usually only one minute but if such attacks are prolonged or repeated they should be treated by the intravenous injection of a small dose of a barbiturate such as pentothal sodium or with intravenous trimethadione (tridione) All physicians especially those not thoroughly familiar with picrotoxin should have such an antidote on hand An attack of convulsions is invariably followed by a state of increased depression and naturally no analeptics of this type should be given for a while An alternative method of administration consists of the continuous infusion of picrotoxin at the rate of 1 mg per minute While good results have also been obtained with this procedure we favor the intermittent technic which we believe provides a greater safeguard against accidental over dosage If the desirable state of increased reflex activity has been attained or slight twitching has followed the last dose of the picrotoxin the amount of the single doses is decreased and the interval between injections is lengthened The aim is now to keep the patient from relapsing into deeper coma and to proceed slowly and carefully with further denarcotization In many instances it will be possible gradually to substitute intramuscular for intravenous picrotoxin administration

While in a normal person 20 mg of picrotoxin may lead to serious toxic symptoms the presence of large amounts of barbiturates in the body results in a vast increase of tolerance to this analeptic drug We have given as much as 5 gm over a period of about 10 days and Newman and Feldman have recently reported the use of more than 14 gm Obviously this does not necessarily mean that these patients could not be saved with less and the object of the physician should be to give only as much picrotoxin as will produce the desired effect However the absence of a toxic action of large doses on the function of other organs as we have frequently ascertained makes it possible to be governed entirely by the degree of the central stimulating effect of picrotoxin during its administration in barbiturate poisoning In patients reacting favorably it still may be necessary to continue treatment around the clock for several days until consciousness is restored On the other hand we have never seen recovery in any patient who failed to show at least some response after several hours of intensive therapy with this stimulant and other supportive therapy Animal experiments by Richards et al have shown that intracisternal injection of picrotoxin is more powerful than the intravenous route and we believe that in desperate cases this procedure may become justified

Metrazol has been used successfully as the sole analeptic drug in cases of severe barbiturate poisoning Androp has described such a case where repeated injections of a 10 per cent solution were given at 15 to 30 minute intervals The single doses varied from 5 to 9 cc In our opinion picrotoxin is the preferable drug for the sustained treatment of severe poisoning because of its experimentally proved more powerful analeptic effect and its clinically longer dura

tion Nevertheless we feel that metrazol has definite indications as follows as an immediate acting respiratory stimulant in the beginning of treatment when respiration is severely depressed or during acute respiratory embarrassment occurring later on in the course of such conditions Obviously artificial respiration is always the first thing to apply Furthermore we have successfully used metrazol injections during the treatment with picrotoxin in order to gauge the depth of depression The procedure is in general the same as that suggested by Alexander, to which we have referred above Incidentally we have found that in the absence of cyanosis the response to a few whiffs of 5 per cent carbon dioxide is also a good indicator of responsiveness of the patient Finally, metrazol is especially valuable in the later stages of a successful treatment where the patient has responded to picrotoxin, is restless but still depressed and will react with signs of overstimulation to increased picrotoxin doses The judicious use of metrazol injected intravenously in doses of 2 to 4 cc will frequently result in further denarcotization Metrazol appears to have a better cortical effect than picrotoxin and we

Recently sympathomimetic amines, especially amphetamine and desoxyephedrine have been recommended for the management of barbiturate poisoning (Freireich and Landsberg) These drugs are not only analeptics but also vasodepressors We believe that they may play a useful role in the treatment of barbiturate poisoning but that they should not be relied on as the sole agents in severe cases They can be successfully employed together with picrotoxin and other stimulants Single doses have ranged from 10 to 20 mg intravenously and such injections can be repeated at hourly intervals Under special circumstances, as much as 40 mg of amphetamine in single doses can be used under careful control of the circulation Because the vasodepressor action of these drugs may exhaust itself with too frequent injections of high doses, the blood pressure response should be checked repeatedly In our opinion special care should be taken to avoid unfavorable circulatory effects in older persons or those suffering from cardiovascular disease These drugs, as ephedrine, are recommended for all patients, in whom the blood pressure fails to rise to normal levels or decreases unduly during the previously described management. Neosynephrin (100 to 200 mg per liter) may be administered by intravenous drip to patients suffering from severe vascular collapse

A new idea for the treatment of barbiturate poisoning was introduced by Taubenhaus and Soskin Since it is known that barbiturates do not interfere with the oxidation of succinate by brain slices in vitro, they suggested the administration of large doses of sodium succinate in barbiturate poisoning At present the practical usefulness of this procedure is controversial In our own experience and in that of many others with whom we have discussed this procedure no convincing effect on the course of this condition was obvious However, Barrett feels that this material exerts a definite respiratory stimulating effect and lightens barbiturate depression He suggests the intravenous use of a 30 per cent sterile solution of disodium succinate hexahydrate in distilled water, which is equivalent to an 18 per cent solution of sodium succinate Such a solution has been made available under the name of soduxin by Brewer and Company of Worcester Mass Barrett advises the immediate intravenous injection of 3 to 4 cc at the rate of 1 cc per second, this is usually followed by coughing Fifteen to 30 gm of the hydrated salt were administered within 15 minutes to adult patients As an alternative method, a 10 per cent solution may be given as intravenous drip infusion over 2 or 3 hours after an initial injection of a few cubic centimeters of the concentrated material If a physician decides to make use of this procedure, he must remember that large doses of sodium are thus given to the patient possibly resulting in an increased tendency for water retention and alkalosis Therefore, proper care must be taken to avoid undue changes in electrolyte balance

In addition to the above mentioned procedures, supportive treatment is of greatest importance Since the patient is comatose, perfect nursing care is mandatory This in-

cludes the prevention of burns by hot-water bottles, etc, catheterization, and the judicious use of intravenous fluids This should be adjusted to produce about 1000 to 1200 cc of urine per day and is best obtained by the administration of dextrose and saline, however, not more than 1 liter of the latter is usually required The tendency to pulmonary edema in severe cases requires prevention of overhydration and the same applies even more so if the suspicion of cerebral edema arises For the first named condition we have sometimes successfully used the subcutaneous injection of pituitary extract preceded by 0 25 to 0 4 mg strophanthin-k or an equivalent amount of ouabain (strophanthin g) intravenously Cerebral edema is usually a bad prognostic sign, but an attempt can be made to influence it by intravenous injection of 50 cc of hypertonic sucrose or sorbitol solutions or the release of spinal fluid if the pressure is increased Fever occurs almost always on the second or third day after the onset of the depression, prophylactic and therapeutic administration of antibiotics is important and the sulfa drugs may be used in therapeutic doses if indicated Parenteral administration of vitamin B complex, and especially vitamin C in doses of 100 to 200 mg daily, is always indicated Oral administration of liquid foods can be begun as soon as the swallowing reflex is definitely re established With the return of consciousness special care on the part of the physicians and nursing personnel is indicated, particularly in patients who had taken the drug with suicidal intent *Psychiatric consultation and supervision* of the patient to prevent him from repeating his attempt are strongly suggested

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BROMIDE INTOXICATION

With few exceptions bromide intoxications are the result of prolonged therapeutic administration of high or occasionally even moderate doses of inorganic bromide preparations Such incidences have been reported *after daily consumption* of 40 to 50 grains of alkali bromides for 14 weeks, or after shorter periods with higher doses

Fatal outcomes are rare but have occurred with blood bromide levels of 325 mg per 100 cc

The symptoms consist chiefly of depres sion ataxia inco ordination of speech hallu cinations and frequently paranoiac ideas Toxic delirium is most liable to develop in persons suffering from a psychoneurosis (Millikan and Paul) Such findings should warn the physician to have a blood bromide determination made even if the patient or members of the family deny bromide medi cation as many nostrums contain this chem ical in a disguised form The so called bromide acne in its various manifestations is quite often absent even in severe cases of chronic bromide poisoning its occurrence is independent of the blood bromide concen tration The bromide level in the blood is normally below 2 5 mg per 100 cc blood The level at which toxic symptoms appear varies considerably persons in a poor nutri tional state in advanced age or suffering from renal dysfunction may show intoxica tion with 75 mg per 100 cc (Angyal) while on the other hand epileptics may show hardly any depression with 100 to 125 mg per 100 cc blood Usually values above 150 mg per 100 cc are definitely indicative of bromide intoxication Alcoholics are also more liable to develop intoxication after in ton

mg of sodium bromide are equal to 116 mg of bromide ion (Detweiler)

Bromides are rapidly absorbed and tend to replace chlorides in the body thus even the gastric juice may contain hydrobromic acid If about 25 to 30 per cent of the body chloride is replaced by bromide definite intoxication is present and fatalities occur above 40 per cent For practical purposes the excretion of chlorides and bromides by the kidneys takes place in proportion to their relative concentration in the blood from this it follows that only small amounts of bromides will leave the body during the first weeks of treatment until considerable amounts have been accumulated

The treatment is directed to reverse the accumulation of bromides by withdrawal of this medication and administration of large amounts of sodium chloride In severe cases with marked restlessness which is some times accompanied by increased cerebro spinal pressure a therapeutic spinal tap is indicated and other sedatives such as paral dehyde or phenobarbital are necessary (Gundry) Adequate nutrition must be pro vided In severe cases sodium chloride may have to be administered intravenously as a 2 5 per cent solution This should be followed by oral administration in doses of 6 to 12 gm daily in divided doses A part may be given in the form of salted foods and the balance in capsules with a sufficient amount of water Some authors claim favorable results by combining this treatment with intramuscular injections of 5 cc of adrenal cortical extract for the first few days It is desirable to follow the blood bromide and blood chloride levels during this treatment Care should be taken not to overload older persons particularly those with circulatory and renal impairment with large amounts of sodium chloride and fluids In such patients a more gradual re placement therapy appears logical Under

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and some clinical similarity of the symptom atology of bromide intoxication and pellagra it has been recently recommended that the conventional sodium chloride therapy be sup plemented with daily doses of 600 to 750 mg of nicotinamide Clinical evidence so far is meager but this approach may be well worth further consideration

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ARSENIC POISONING

The toxicologic importance of arsenic is given by the various forms in which it may lead to poisonings These may be accidental criminal suicidal medicinal or occupational Arsenous oxide Fowler s solution and the gas arsine are the most important inorganic compounds of the organic forms the various arsenicals used in chemotherapy are of special interest Arsenic-containing insecticides certain dyes and paints and various industrial uses may lead to accidental or occupational poisoning Arsenic in various forms can cause acute or chronic intoxication

Acute Poisoning While intoxication with inorganic arsenicals may occur by absorption from the skin the most frequent route is the digestive tract followed by inhalation of dust or the gaseous arsine or by injection of

[illegible]

that the most dramatic action of inorganic arsenicals is their profound paralyzing effect on the capillaries especially those of the intestinal tract Thus violent diarrhea followed by dehydration and general vascular collapse are the predominant features Usually a few hours elapse before symptoms appear after ingestion but with overwhelming doses coma unconsciousness and death can follow quickly after the intake of the poison without gastro intestinal symptoms

The treatment should be directed to the removal of unabsorbed poison by washing the stomach repeatedly Arsenous oxide tends to cling to the folds of the gastric mucosa making its removal difficult The treatment of poisoning with arsenicals has been radically changed by the discovery of BAL which will be discussed in detail later

[illegible]

stomach has been evacuated one may administer a freshly prepared ferric hydroxide suspension This is done by diluting 15 cc (½ oz) of tincture of ferric chloride with

[illegible]

tially used for the gastric lavage and later administered in teaspoonful doses with milk. This mixture has at least some absorbent effect and will thus retard absorption of the arsenic Activated charcoal can be used instead A laxative dose of magnesium sulfate or castor oil should be given to hasten the elimination through the bowel The symptoms following vascular collapse require energetic treatment by the administration of vasoconstrictors e g epinephrine or related compounds as well as a central stimulant such as nikethamide (coramine) or metrazol It appears reasonable to prevent dehydration by intravenous fluid administration and one would expect plasma or gelatin infusions to be of value The mortality from acute arsenic poisoning in the pre BAL era ranged from 50 to 75 per cent Death has followed the ingestion of as little as 60 mg arsenous trioxide 0 1 to 0 3 gm were usually fatal but larger doses have not always been fatal

Pharmacologic Properties of BAL and Its Use in the Therapy of Arsenic Poisonings It has been known for some 20 years that the toxicity of many heavy metals and arsenic is at least partially due to their combination with the sulfhydryl groups of the enzyme proteins Voegtlin et al showed in 1923 that certain substances containing sulfhydryl groups could counteract the toxic action both in vitro and in vivo British investigators who were seeking antidotes against the arsenic containing war gas lewisite developed several compounds of this nature and found that the dithiols are even more effective than the monothiols (Peters et al Stocken and Thompson) The chemical deemed most suitable was 2 3 dimercaptopropanol briefly called BAL an abbreviation of British anti lewisite

Extensive biochemical and pharmacologic studies with this material carried out in England and in the United States have shown that BAL not only neutralizes arsenic and certain heavy metals in vivo by preventing the attachment of the poison with vital cell enzymes but within limits can even revert such combination after it has occurred

Aqueous solutions of BAL are unstable and a 10 per cent solution in peanut oil containing 20 per cent benzyl benzoate (Hynson Westcott and Dunning) is now almost

universally used for intramuscular injection BAL is by no means nontoxic In animals toxic doses produce lacrimation, muscular in co-ordination finally generalized convulsions and death There are no typical anatomic findings Side effects even with therapeutic doses in man are not uncommon and are noted in about 15 per cent of the cases with doses of 4 mg per kilogram of body weight and in more than 50 per cent at 5 mg per kilogram Aside from moderate pain at the site of injection and the rare occurrence of sterile abscesses, mild systemic effects con sist of lacrimation, salivation a burning feel ing in the mouth and eyes anxiety, and a moderate rise of blood pressure These symptoms disappear usually within 1 to 1½ hours after intramuscular injection only ex ceptionally lasting longer than 4 hours Woody and Kometany observed a child who by mistake received two doses of 8 mg per kilogram of BAL each at 3 hour intervals Symptoms as described above disappeared within an hour after the first injection they were more severe after the second and an attack of convulsions followed by depression occurred, but the child recovered completely without sequelae BAL is also absorbed through the skin, as has been proved both experimentally in animals and clinically in humans However, it is somewhat irritating, causing local erythema, whealing and itch ing If the skin had been damaged pre viously by mustard gas dermatitis occurred in 66 per cent after local application Nine teen per cent of the patients who were treated with the 5 per cent BAL ointment developed various forms of skin reactions of an allergic nature Cutaneous sensitivity can also be produced by intramuscular in jections It is agreed by most investigators that BAL administration increases the out put of arsenic in the urine This follows both the [illegible]

cated and it is still not fully explained why animals receiving nonfatal doses of sodium arsenite together with BAL developed se vere stimulation of the central nervous sys tem which does not occur with either of the two compounds alone (Koppanyi and Sperling) Thus it is theoretically possible that the use of BAL in cases of poisoning with arsenites such as Fowler's solution may develop toxic side effects However, this should not deter one from the use of BAL in cases of serious poisoning with such prep arations

Clinically BAL has been used successfully in various forms of arsenic poisoning Woody and Kometani used it in 42 children, half of whom had probably taken lethal amounts of arsenic containing substances There were no fatalities in this series and the symptoms of poisonings were under control within 12 hours after institution of the BAL therapy The drug was likewise successfully applied in 2 patients who by error had received 400 and 600 mg of mapharsen, while another died after 1200 mg, probably because therapy was discontinued too early (Eagle and Magnusen) Other successful uses in clude arsenic encephalitis, blood dyscrasias following arsenical therapy, optic complica tions, and exfoliative dermatitis caused by injection of arsenicals In the latter condition the duration of severe symptoms was cut about in half with a particularly favorable effect on the oozing form of toxic dermatitis

The Council on Pharmacy and Chemistry of the A M A has suggested the following treatment schedules for the use of intramus cular BAL injections in severe arsenical poisonings, especially the encephalitic type, exfoliative dermatitis, overdosage of arseni cals or blood dyscrasias A dose of 3 mg of BAL per kilogram in oil should be injected six times a day at intervals of 4 hours On the third day four injections are recom mended and for the following 10 days two daily injections or until recovery occurs In milder cases only four daily injections of 2 5 mg per kilogram each for the first 2 days followed by two injections on the third day and one daily injection for the next 10 days In serious cases it may be desirable to exceed these recommendations for the first two doses as it has been found that four doses of 5 mg per kilogram each can be given at 4 hour intervals without serious acute or cumulative toxic effects Administration of 25 mg ephedrine sulfate by mouth half an hour prior to the injection of BAL reduces the toxic side effects (Tye and Siegel) Ad ministration of BAL ointment (5 per cent) to the skin in exfoliative arsenical derma titis or of a suitable ointment of aqueous

solution to the eye in case of lewisite burns has been investigated but the clinical experience is still limited and such preparations are not commonly available The inunction of BAL ointments in these cases is painful and this factor, as well as the possibility of sensitization, seems to militate against the routine use of this therapy Eagle is undecided about the usefulness of BAL in jaundice occurring during treatment with arsenicals, results were good in about half of the cases The causative role of arsenic in this condition has been questioned by others It should be used with care in patients with impaired liver function (Cameron et al)

BAL is apparently not effective in preventing the dangerous hemolytic reaction following poisoning by arsine The ethyl ether derivative of BAL shows an antagonistic effect in animals but its great toxicity seems to preclude its use in humans There is no definite evidence in one way or another whether or not BAL will favorably affect late toxic effects of arsine Management of arsine poisoning is still unsatisfactory Oxygen should be administered together with other symptomatic treatment Repeated blood transfusions may become necessary and the patient should be protected as far as possible against the consequences of the hemolytic action of this poison This should include ample fluid administration to prevent anuria and proper treatment of this condition if it should develop Peritoneal lavage may be useful to prevent fatal azotemia

For prevention and management of the various forms of acute side effects during treatment with arsenicals, such as nitritoid reactions and therapeutic shock, the reader is referred to textbooks on syphilology.

Chronic Poisoning With the decrease of the use of arsenic in therapeutics as well as in industry, the incidence of chronic poisoning appears to be on the decline The diagnosis of chronic arsenic intoxication can be difficult because of the various manifestations which resemble frequently endogenous conditions such as gastro intestinal disturbances, chronic bronchitis, skin disorders, polyneuritis and degenerative changes of the parenchymatous organs The treatment is based on elimination of the cause and general supportive and symptomatic treatment Daily intravenous injections of 0 5 gm. of sodium thiosulfate may be tried The possible effect of BAL remains to be established

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MERCURY POISONING

Of accidental or suicidal poisonings with mercury, the ones following the ingestion of soluble mercury salts, especially bichloride

of mercury are the most important Fortunately this compound leads to prompt vomiting in many instances thus reducing somewhat the danger of serious poisoning Nevertheless such intoxication must always be considered serious especially so because of the quick absorption of these salts from the mucous membranes If vomiting does not occur promptly the prognosis is serious with 1 0 gm or more of bichloride of mercury This applies equally to other soluble salts Whether or not vomiting has occurred the stomach must be evacuated immediately by gastric lavage or induction of vomiting followed by lavage The washing fluid should contain about 1 teaspoonful of sodium bicarbonate per pint Sodium chloride solutions by mouth are to be avoided because they favor the solubility of bichloride of mercury Administration of skimmed milk (fat increases absorption) or the white of several eggs has been recommended and there is some experimental evidence that charcoal binds mercury salts It must be kept in mind that these procedures are based on a temporary absorption of the poison which will not prevent its ultimate absorption Thus quick elimination by stomach washing or less reliably by administration of a saline laxative must supplement such temporary expedients

As in arsenic poisoning the treatment of mercury poisoning has been revolutionized by the introduction of BAL The basic principles have been discussed under arsenic poisoning and likewise arsenic treatment should be early and vigorous Somewhat higher initial doses than those routinely used in arsenic poisoning are recommended in the treatment of intoxication with mercury salts The first injection should consist of 5

about 4 hours In severe cases another such dose is given within the first 12 hours after start of the treatment On the second day two doses of 2 5 mg per kilogram are administered and on the third day one dose Further continuation will depend on individual circumstances A slightly different scheme has been recommended by Batson and Peterson who use 3 5 to 4 5 mg per kilogram as the initial dose followed in 2 hours by 2 to 3 mg

Longcope and Luetscher did not lose any of the 37 patients in whom BAL injections

supplemented by additional supportive measures

If BAL is not immediately available an attempt should be made to use one of the following treatments until BAL administration can be instituted Sodium formaldehyde sulfoxylate has been recommended by Rosenthal and by others (Wolpaw and Alpers) A freshly prepared 5 per cent solution is used for stomach lavage and 200 cc of it are given orally This may be supplemented by slow injection (20 to 30 minutes) of 10 gm of pure salt in 200 cc of distilled water This may be repeated 4 to 6 hours later As a second choice sodium thiosulfate can be given orally in amounts of 1 to 2 gm and intravenously by injecting 20 cc of a 5 per cent solution These procedures will probably affect only mercury which is not yet fixed in the tissue but they should be carried out promptly until systemic BAL treatment can be started

In cases of severe poisoning it will be necessary to treat shock by the established methods including administration of blood plasma and intravenous crystalloid fluids It is well known that mercury salts damage the kidney and also cause colitis because they are partially excreted through the intestine For the latter repeated colonic flushing has been recommended using either a 1 1000 solution of sodium formaldehyde sulfoxylate or one of 0 5 gm of calcium sulfide per liter The severe necrotizing nephrosis is the most dangerous consequence of mercury poisoning and may lead to death by anuria within a few days Albuminuria with the appearance of casts and blood are the early signs of kidney involvement Blood chlorides and N P N should be carefully watched and a consistent drop of the former and a rise of the latter are prognostically unfavorable signs

The management of this condition is in general the same as that of anurias from other causes. Peritoneal lavage may be helpful in preventing fatal azotemia. This procedure has been used successfully by Batson and Peterson and their publication should be consulted for the composition of the washing solution and the technic of its administration. The question of the usefulness of kidney decapsulation has not been completely settled as yet, but does not seem to be favored by recent investigators.

Recently a number of serious and sometimes fatal accidents have been reported following the intravenous injection of various mercurial diuretics. In some instances circulatory disturbances, collapse, fever or anaphylactoid reactions have occurred. Fatalities were usually due to cardiac effects, probably the occurrence of ventricular fibrillation, but respiratory failure or anaphylactic shock may have been responsible for a few. The change from one preparation to another eliminates the intolerance for some patients (Barker et al., DeGraff and Nadler). The treatment of the acute episode is entirely symptomatic. Intramuscular injection of these drugs is much safer and is advisable unless particular reasons require the intravenous route.

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LEAD POISONING

Lead may enter the human body accidentally, usually due to occupational exposure: (1) by inhalation of lead-containing dust or fumes as metal salts or organic lead compounds; (2) by ingestion; (3) by absorption through the skin, usually of tetraethyl lead, the well-known "anti-knock" fluid in gasoline. The first named route is today the most common cause in the United States. Occasionally other mechanisms, such as absorption from embedded lead shot, are involved. It should be remembered that exposure to lead does not necessarily mean lead poisoning. With the so-called normal diet the average person takes in small amounts of lead but absorption from the intestinal tract is poor and as long as the excretion keeps up with absorption poisoning does not occur. In contrast absorption from the respiratory tract is much more extensive.

Laboratory methods, if conducted by experienced personnel and judged in connection with other factors, are of great diagnostic help. Briefly the following values indicate a dangerous degree of exposure: basophil "stippling" in more than 800 to 1000 red cells per 1 000 000; a fecal lead content of more

per liter of whole blood indicate lead exposure and suggest poisoning at 1.0 mg. per liter or higher (Kehoe et al.).

It is advisable that these determinations be made while the patient is still under exposure because the findings are subject to rapid change after removal from his usual occupational surroundings. Workers may have laboratory findings in the above mentioned order of magnitude without clinical symptoms, but abnormal findings are a warning sign and are supportive evidence in the presence of clinical disease. On the other hand, the absence of abnormal amounts of lead in the urine, blood and feces on repeated examination under suitable conditions are incompatible with the diagnosis of lead poisoning. The well-known lead line in the gums can exist in exposed persons without evidence of sickness. Details of the clinical symptomatology and diagnosis of lead poisoning are not discussed here.

If the abdominal pain which is usually the outstanding symptom is severe hospitalization is advised Intravenous calcium therapy should be instituted by injection of 10 cc of calcium gluconate of gluconogalactogluconate (neocalglucone) or 5 cc of 10 per cent calcium chloride solution Four to 5 minutes should be used for each injection these must be repeated several times during the next few days until abdominal pain is under control The first two preparations named can be given intramuscularly after the acute phase has been overcome Wilentz recommends "around the clock" intravenous calcium therapy for the first period in all

[illegible]
tried to break the paroxysmal spasm In rare instances the use of narcotics may become unavoidable and it appears reasonable to try first meperidine hydrochloride (demerol) in doses of 100 mg subcutaneously before resorting to morphine Hot applications to the abdomen are usually well tolerated

After the acute attack has been controlled the bowels should be emptied by giving ½ to 1 oz of magnesium sulfate and a mild laxative is recommended during the following days to combat constipation In most cases it will be possible to control the colic in 1 or 2 days Parenteral calcium therapy is gradually substituted by oral administration as 1 gm calcium gluconate four times daily The diet should contain ample milk calcium and phosphorus for the next several weeks Formation of kidney stones under this treatment has been seen occasionally (Cotter) Iron preparations are indicated only in the second period of the treatment in order to combat anemia Naturally all possibilities of exposure to lead should be excluded and outdoor exercise and a nutritious diet with the addition of vitamins will help to overcome weakness and malaise

The intestinal symptoms disappear at the latest within 2 to 4 months without leaving permanent sequelae but neuritic complications can persist for a considerably longer period

It has been assumed for some time that lead and calcium follow an essentially similar metabolic behavior in the body (Aug) Accordingly procedures favoring calcium retention will also tend to deposit lead especially in the bones which are by far the most important storage place during prolonged exposure to this metal Conversely mobilization of calcium will result in "de leading with increased urinary lead excretion During the acute phase the therapy as we have discussed it is directed to removing the lead from the circulation and favors its immobilization in the skeleton

The long favored procedure of "de leading the patient after the acute symptoms have completely subsided (never before) has recently lost ground Consequently we shall discuss this form of treatment only briefly In general it is based on bringing the patient into negative calcium balance which is thought to release lead from the tissues into the blood stream followed by increased excretion through the kidneys For this purpose the patient is placed on a low calcium diet avoiding all milk milk products and green vegetables while meat and colored vegetables butter and fat are permitted Three to 4 days later ammonium chloride is added with an initial dose of 1 gm three times daily This is given as a solution with ample water during the meals or in the form of enteric coated tablets to avoid gastric irritation If tolerated the ammonium chloride intake can be gradually stepped up to 8 gm daily The patient may have some nausea loss of appetite and weight but these symptoms disappear on withdrawal or reduction of the medication Strict medical supervision is necessary and the occurrence of acute attacks of lead colic under this treatment necessitates its discontinuance A 3 or 4 week employment of this regimen is recommended. Other schemes use potassium iodide (0 5 to 2 5 gm per day) sodium bicarbonate (20 to 40 gm daily) or other agents with the idea of lead mobilization After the patient has finished one course of de leading he is placed on a high calcium diet to replenish his calcium stores and the whole procedure may be repeated for a few times at intervals (Hunter)

One of the recent innovations is the use of 2 3 dimercaptopropanol (BAL) This sub

stance is known to possess a great affinity to certain metals and its detoxifying properties are discussed in connection with its use in mercury and arsenic poisoning Telfer has used BAL in lead poisoning giving it in doses of 1 9 mg per kilogram for 5 days or even longer in some instances Twelve such injections were given This was followed 17 days later by four daily injections of 2 5 mg of BAL per kilogram for 19 doses Kehoe *in a recent study* has reviewed this procedure and reported on the results obtained with the injection of 5 mg of BAL per kilogram This resulted in a decrease of the blood lead content and a 34 fold increased lead output in the urine Apparently BAL releases the lead from its combination with the red cells but no extensive de leading of the body appears to take place

Recent investigators (Kehoe Wilentz) agree that only insignificant amounts of lead are released from the body by any of the de leading procedures which in addition are potentially harmful While the final decision on this whole subject has certainly not yet been reached the present tendency does not favor de leading with or without the use of BAL as a routine procedure in the management of chronic lead intoxication but it must still be considered permissible in individual cases

Acute lead poisoning due to consumption of soluble lead salts is treated by gastric lavage followed by administration of a laxative dose of magnesium sulfate Intravenous calcium therapy and other management should be instituted as outlined above Sollmann *states that* 10 gm of soluble lead salts have caused death while as much as 30 gm have been survived There is no present clinical experience of the possible effect of BAL on acute lead poisoning and animal experiments do not indicate that it is of value (Weatherall)

The severe acute encephalopathy which may follow especially after the inhalation of tetra ethyl lead can lead to toxic delirium and a variety of nervous and mental symptoms Intravenous infusions of 2 to 4 gm magnesium sulfate in 2 per cent solution combined with oral doses of pentobarbital as indicated have been *recommended* (Machle) Other symptomatic treatment is instituted as required followed by the management of lead poisoning as described above

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MANAGEMENT OF BITES BY DOMESTIC SNAKES

The venom of the North American snakes possesses various toxic components which affect the tissues locally by causing swelling edema *and gangrene as well as* severe systemic effects on the respiratory center nervous system muscles heart blood and circulation Mortality without specific treatment is estimated at about 11 per cent with it at about one fourth of this figure Death may occur several hours or a few days after the bite The generally accepted emergency treatment consists of the application of a tourniquet a few inches above the bite The constriction should be strong enough to weaken but not to abolish completely the pulse peripheral to it The tourniquet should be released for 3 minutes every half hour until antivenin can be administered An antiseptic is applied to the bite and crosswise incisions ½ in long and ¼ in deep

are made with a sharp knife avoiding pos sible injuries to underlying larger blood

should be rinsed repeatedly with a dilute solution of potassium permanganate which destroys the venom Suction should be re peated for 15 to 20 minutes every hour If swelling progresses the tourniquet has to be moved farther centrally and additional in cisions can be made to which suction can also be applied Applications with strong salt or epsom salt solutions are made to encour age drainage The patients must be kept as quiet as possible and should not be allowed to walk Small doses of analgesics or seda tives can be given to relieve pain and anxiety and copious intravenous infusions with saline or blood are suggested for severe cases Contrary to popular belief the adminis tration of alcohol is inadvisable The use of stimulants is necessary in cases of collapse

An effective specific antidote has been prepared under the name of antivenin by Wyeth Inc of Philadelphia which is a poly valent equine hyperimmune serum against rattlesnake copperhead and moccasin ven oms but not against that of the coral snake which is native to the southern United States This serum is available in a dried form which is stable for at least 5 years It may still be lifesaving in desperately sick patients Large doses (75 cc) and repeated administration may be necessary Because of its preparation from horse serum the patient must be tested for hypersensitivity and it may be wise to have an intravenously injectable antihista minic and epinephrine available

Detailed instructions regarding dosage route of administration and precautions are contained in the directions which accom pany each package of antivenin The manu facturer has also prepared an instructive booklet on the treatment of snake bites on which we have drawn freely for this outline

RICHARD K RICHARDS

BLACK WIDOW SPIDER BITE

The black widow spider (Latrodectus mactans) occurs in the United States chiefly in the southern and the western coastal re gions but occasionally in other parts of this country and in Canada The poison is of protein like nature and by weight is more toxic than that of the rattlesnake Neverthe less fatalities seem to be exceedingly rare The bite is followed within 15 minutes by violent pain over the whole body nausea, and even delirium and convulsions Marked abdominal rigidity may sometimes lead to confusion with intra abdominal emergencies The blood pressure is usually elevated and the occurrence of a peculiar burning sensa tion of the soles of the feet 24 hours after the bite has been reported as a typical symp tom (Frank)

The treatment is both specific and symp tomatic The former can be carried out by prompt injection of 1 to 2 units of Latro dectus mactans antivenin (Wyeth Inc Philadelphia) Tests for sensitivity are made before the intramuscular injection of this antiserum and the precautions and instruc- tions accompanying the package must be carefully observed The preparation is avail able in a dried state and will keep for about 5 years Usually it will take a few hours be fore this treatment becomes effective In the meantime and if no antiserum is available prompt symptomatic treatment is obligatory The results obtained with the various pro cedures are not uniform and the various in vestigators favor different methods A brief résume of the most frequently applied pro cedures follows

Intravenous injection of 10 cc of a 10 per cent solution of calcium gluconate or calcium chloride is favored by many authors This dose may have to be repeated several times within 2 to 4 hour intervals Magnesium sul fate in a 6 to 10 per cent solution may be given by slow intravenous injection up to 20 cc per dose under careful observation (Ginsburg) It must be kept in mind that large amounts of magnesium may seriously depress respiration Such accidents must be promptly counteracted by the physiologic antagonist of magnesium ions namely, cal cium salts given intravenously and the hypo- dermic injection of neostigmine methylsul fate (prostigmine) in doses of 0 5 mg Artificial respiration may be instituted if necessary Often morphine is indispensable to combat the severe pain This can be ad ministered in doses of ¼ to ½ grain (15 to 30 mg), subcutaneously or ⅛ grain (7 5 mg),

intravenously at a slow rate In children ½ grain (30 mg) of codeine phosphate sub cutaneously has been found satisfactory Morphine and magnesium are synergistic in their depressant effect on the respiration and this should be kept in mind in directing the treatment

A recent suggestion which is still in need of more extensive confirmation is the intra muscular injection of 2 cc of 1/2000 neostig mine methylsulfate (prostigmine methylsul fate) with 1/150 grain (0 4 mg) of atropine sulfate This has been reported to have brought relief within 15 minutes and the dose can be repeated four times at 4 hour intervals (Bell and Boone Beck)

While the pain usually decreases without sequelae milder attacks may recur from 1 to 4 days after the bite The average dura tion is 30 to 40 hours The use of hot baths has been found beneficial in rel eving tempo rarily the marked muscular pain It should be noted that in contrast to snake bite no local treatment such as suction or incis on is advised Simple cleansing and dressing are sufficient

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DISEASES OF THE NERVOUS SYSTEM

A THERAPEUTIC APPROACH TO PSYCHOSOMATIC PROBLEMS

The first thing to do if one is to treat psychosomatic problems successfully is to make the correct diagnosis Naturally one does not help a patient with let us say hysterical bloating if one operates for a sup posed intestinal obstruction

The Need for a Good History Essential in the treatment of persons with nervous diseases is the taking of a good history, and especially a history which causes the patient to see how he or she got into difficulties Occasionally, after the physician has taken [illegible] now that it is all up to me and I'll go home and do what I have to do to straighten things out"

Another way in which a physician almost cures a nervous patient as he takes a good history is by showing that he knows the disease well A badly worried person is cheered and encouraged when he sees that his disease is not so rare and inexplicable as he thought it was It was the unknown that was frightening him

Often all the physician has to do to help a woman with a so called mucous colitis is to tell her that her story is an old one that he has heard a thousand times before He knows the syndrome well and he has never seen anyone come to a bad end because of it It never turned into cancer, true colitis, or anything else Often this is what the pa tient wanted to know She can now put up with the discomforts since she knows they are harmless and will recur whenever she gets tense, excitable, or upset

Similarly, the person with severe sick head aches is often much frightened by them. As a result she is much better when the doctor says "This is a common and well known syndrome It is not produced by a brain tumor or anything serious, and it will never bring you to a bad end It is due to a nervous storm which opens up the arteries in the brain and allows the blood to go pounding through them You will have much fewer attacks if you can avoid fatigue and nervous strain" Once the patient is convinced of this, she will be half cured The person who fears heart disease can also be almost cured by a good history which calls his attention to the fact that he has a good wind, so good that he can go hunting and walk miles without dis- tress This is the best proof that he has an efficient heart

There are other ways in which the taking of a good history helps Today, with physi cians as busy as they are and with consultant practice as mechanized as it has become, nervous patients are distressed when they are not given time in which to tell their whole story Too often they are asked only a few questions and then are sent to laboratories and roentgenologic departments and special ists for examinations

The Examination Not infrequently an- other complete examination is not what the person needs, especially when the diagnosis is obvious from the history, and when dur- ing the year, several such examinations were made, all with negative results To most in- ternists today the fact that the person has been carefully examined usually means noth- ing they want their own tests and roent- genograms made and they refuse to see the patient until these are all repeated In some cases of course, some tests should be re peated but when a woman comes with a typical nervous regurgitation, a bad emo- tional problem, and a lot of roentgenograms showing a beautifully functioning gallblad- der, it is hard to see why they should be taken over again It would seem better, in such a case, to spend little time on examina- tions and much time in explaining the woman's problem to her and trying to find some way in which she can [illegible] from

difficult and uncomfortable situation Only in this way will the *physician give her good* value for the money she pays him

In most cases of course, the physician will want the patient to have at least one good examination, because even an insane man can have a carcinoma somewhere All I am objecting to is the senseless repetition of tests that have already been well made and have shown, as was to be expected, *that there is* nothing wrong in the thorax and abdomen

Obviously, a good careful examination has great therapeutic value If the results are negative, a sane patient is immediately cheered and reassured He may know that he is neurotic or psychoneurotic or troubled and that because of this he can be ill, but he has had the sense to realize that in addition to a neurosis he could have had a carcinoma or a peptic ulcer or a brain tumor *Once relieved of this anxiety he may return* home cured

The Need for Spending Time Today we physicians are not always giving our nervous patients a square deal As already noted we are not giving them enough time in which to tell their stories of unhappiness and tragedy and frustration Often if a patient *could get this story off his chest* he would be helped There certainly is such a thing as mental purgation, and the priest helps many a troubled person when he listens to his confession In the old days we physicians also used this technic, but today too many of us feel that we have no time for it Even the psychiatrists are becoming so busy and having such enormous demands made upon their time that patients who have been to some of them are complaining that in their offices they *did not have a chance* to tell their story They were either just talked to or else turned over to assistants for mental testing This cannot work well *because there* never will be any good substitute for conversation between physician and patient, conversation in which the patient does most of the talking

The physician who limits his interviews to 5 or 10 minutes a patient can never do much in the way of recognizing or curing *functional troubles* Even when he gets the correct hunch that the disease is a neurosis and tells the patient it is, he will fail to cure because he has not taken *time either to con*vince the person he is right, or to answer *all his objections*, or to tell him what to do to get well

Some Physicians Are Born to be Psychotherapists There are some men and women with a kindly and sympathetic face to whom men and women *can easily tell* their troubles This explains why one physician will quickly get the all important story *of, perhaps, worrisome* sexual adventures or sins, when several others failed to get it The physician who draws out his patients' story of tragedy or unhappiness in a kindly and sympathetic way, and particularly the one who has a philosophic outlook will be curing as he listens He will be radiating confidence and hope Some men with a dynamic or commanding *personality have a strong influ*ence on others, they are born leaders Naturally when such a man goes into medicine he *is likely to be very successful* He can cure hysteria with a bit of suggestion or a quick command, and he can induce many a sick

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assistants about him It helps greatly if he has a big reputation and a number of patients always in his waiting room

Many physicians are by nature and temperament much too taciturn ever to be helpful to persons with nervous troubles They will not take time to explain to their patients in simple English what was found or not found and what these things mean, and hence the still worried patients keep traveling about, dissatisfied and unhelped They were dismissed perhaps with only a few words to the effect that "there is nothing the matter Especially when a person is fearful *that he has a cancer of the stomach* or the colon, the doctor should show him his roentgenograms and point out to him the perfectly normal *outlines of the organs* He should show him the results of all his tests and explain why they were performed, what they mean, and why they are so reassuring When this sort of thing is well done the patient may lose his fear and go home cured

During this process of showing the results of tests, the wise physician will not tell a terribly worrisome patient that he has a func

tional heart murmur or a few changes in his electrocardiogram a spastic colon or a few diverticula on it a ptosed stomach or things of that nature If the physician tells the patient of these little variations from normal he and others during the following years may have to spend hours of time trying to explain their lack of significance and to repair the damage done

Explaining How a Person with Nothing Wrong Can Be Very Ill The next thing that must be done and done expertly is to show the patient how and why a person with negative findings can still be miserable and full of pain It helps most to give examples understandable to the patient of how a person can vomit or get headache nausea frequent urination diarrhea trembling palpitation or faintness under the influence of acute fear or excitement or emotion Then one can say Can t you see now why you who have chronic fear which is worry should suffer too from the effects of your emotion?"

One can explain also how when the brain is too excited undesired influences spread out through the body and as a result the nerves play tricks with a normal heart stomach bowel bladder or skin Occasionally one can point out to a jittery or depressed man some of whose relatives were insane that what he is suffering from is probably his small share of the family curse Often one has to explain to the constitutionally frail person the nature of his illness and what he can do to live with it fairly successfully

Taking Away Placebos of Diagnosis and Treatment One of the first and most important things to do if one is really going to help a psychoneurotic patient is to take away the placebos of diagnosis and treatment which have been given him by the physicians he has already seen Many persons will not like this process and some will persist in clinging to their placebos If they choose to do this they had better be dismissed because the physician who likes really to help his patients will with them largely waste his time For instance let us suppose the phys[illegible] pressive [illegible] een up [illegible] dly in sane mother before her so long as she believes that the chronic ache in her loin is due to a dropped right kidney a kinked ureter or a Hunner stricture nothing curative can be done for her However if she is made to see that she gets the ache every time she goes into a depression or every time her disliked in laws come to visit her or whenever she stands too long or gets too tired or has a spell of insomnia then something can be done for her

One must also take away the placebos of treatment from many nervous persons So long as a man with harmless extrasystoles keeps taking digitalis quinidine or aminophylline every time he is a little frightened or tired he cannot be cured He can become happy and efficient again only if he accepts the physician s view that the extrasystoles are harmless that the heart is normal that irritable nerves are playing tricks with it that they do this when he is tired or upset and that he needs no heart medicine Only as he learns to disregard the extrasystoles can he be a well man

I like what Austen Riggs used to say to a woman when on leaving his sanatorium she came to thank him for having cured her "No said he You ve cured yourself I only helped you to understand" There are thousands of persons who will cure themselves if we physicians will only help them to understand what their real situation is

The Patient Who Keeps Shopping About and Getting Frightened There are many persons full of fear of heart disease cancer or something who cannot be helped so long as they keep shopping about from one doctor to another I always say to the psychopathically anxious man who likes to [illegible]

over some little notching and slurring and who with his bad diagnosis and prognosis will scare you half to death!

Sometimes I say to such a patient "I referred you to a splendid heart specialist and he told you you have a normal electrocardiogram and a typical cardiac neurosis Why not accept his statement and be happy?" Unfortunately the man s doubts will usually return and then he will be no more able to keep away from an electro-

cardiograph than a dipsomaniac is able to keep away from a bottle of whisky And to such a patient an electrocardiogram interpreted by a chiropractor *has the same* significance as one interpreted by a nationally famous cardiologist

On Changing a Person's Personality One reads all the time, in psychiatric journals and books that the physician must remodel the patient s personality I wonder if it ever can be done I even wonder if anyone ever wants his personality changed Many, of course, would like not to be so tense jittery, nervous, or unable to fit into society, or to love or be loved but it s hard for them to mend their ways Much depends on the *person's intelligence and his degree of in*sight into the situation I never spend time trying to make over the person who lacks intelligence, who refuses to listen to me who refuses to accept my view of the situation, who insists on my curing him with a bottle of medicine, who is completely selfish and self centered or who was obviously born to be a psychopath a misfit and a bad actor

Some Persons Cannot Be Helped I will work hard to help the intelligent person who has good insight, who is struggling hard to mend his ways and who seems willing *and even glad to be reassured* The man or woman who seems to hate to be reassured is usually not worth working with Fortunately, long ago, I learned the futility and folly of trying to cure someone against his will

As I have said the person with intelligence and a desire to get well can often be helped He must try hard not to waste his energies on conflicts with himself or with *others and* he must learn to hoard his energies Often he must get *more rest* he may need a vacation, he may need to go to bed earlier and sleep longer and he must try to stop doing many of the things that are hurting him and making him tired and upset Many a tired, nervous housewife needs a maid much more than she needs a physician

Things That Can Be Done Some persons have to take a long vacation, some have to change occupation, and some women will have to separate *from an abusive or alcoholic* husband Others straighten out when they see clearly that their illness is due to some *unhappy* situation or unwise way of living Occasionally I get a letter from a woman who says, "I had a rebirth after talking to you, and I feel like a new person I saw what a mess I was making of my life, and I saw *how I could behave myself* better I saw where I was *using my pains to get my own* way and to keep from facing unpleasant facts I saw, as you said, that I would *never* bring myself to divorce my husband so I settled down to be more contented in my home" This is the sort of thing that a sensible woman can do for herself

The wise physician can tell pretty quickly what type of patient he can help and what type he cannot help As I have said among those he cannot help are the highly opinionated ones who know it all and will hardly *listen to what he says* Many are caught in a miserable trap from which neither they nor I can see any way of escape I'm thinking of, let us say, a secretary who is tired out working in an unpleasant job but who cannot quit because at home she has an old arteriosclerotic, and ailing mother who has to be cared for

Because of these difficult situations in which our patients find themselves we physicians must always make our advice practical It's useless to tell the poor scrubwoman with half a dozen fatherless children to go to *Florida for the winter* Sometimes however by talking to the patient one can find out certain things that he can do in order to get some rest and some relief

Often one of the first things one has to do with a nervous woman is to make her see that there is nothing to be ashamed of in being tense and hypersensitive *She might even be proud of her sensitiveness and reac*tiveness, especially if they enable her to be *a good musician or artist or an interesting* companion to her husband In many cases I have to point out to a patient that she is hypersensitive and overreactive that her knee jerks are tremendously exaggerated and that any person who reacts as violently to every little stimulus must be tired by the end of the day

As one would expect, the physician who has suffered from nervousness can cure nervous persons much more easily than can one who has never suffered in this way The stolid insensitive physician finds it hard to understand how nervous persons can be so "silly" He may have no patience *with them*

and no desire to listen to their tales of woe He may even think they are making their illness out of whole cloth Naturally when a woman discovers that her physician has also suffered from nervousness she is much easier in her mind and more willing to talk because she knows she will not be sneered at or called offensive names

The Value of Optimism It is always good if the physician is an optimist Too many of us are inclined to pessimism and hence we often fail to cure For instance if a man comes in frightened because he has been told that he has had a coronary thrombosis it is wise to tell him of those thousands of men who are still at work 10 and 15 years after such an incident Sometimes an elderly person comes in much frightened because he has had a slight stroke Because of some folk idea he expects in the next few months to have another and then the third big one that will kill him I promptly tell him of patients I have known who after a little or a fairly big stroke waited 15 years for another one I tell of a man I knew who lived 30 years after he had had several little strokes severe enough to cause his retirement from business When a patient comes in much frightened about hypertension I tell of some of the many persons I have known who with a systolic pressure over 200 mm of mercury lived on for 15 or 20 years comfortably enough Why should not the patient know of these cases? Why should he be informed only of the disasters which can happen to him?

The Need for Positive Statements As I have already remarked one of the worst features of medical treatment is the tendency of many physicians to sidestep unqualifiedly re

that he can walk 20 blocks without discomfort The electrocardiogram shows no changes to indicate myocardial damage Under these circumstances my colleague feel

I can find you have absolutely no sign of heart disease I suspect your physician mistook for something serious little changes in your electrocardiogram which in our experience are of no consequence They are the results of age like your gray hair Go ahead now and enjoy life Walk along the street cheerfully as you have always done Play golf if you feel like it and do not worry about your heart"

With this positive statement many a pa would ct him in had hedged and said I think you re all right but you had better play safe Here is some digitalis and don t go upstairs fast don t walk much don t play golf and don t drive your car"

Similarly no physician can cure hysteria unless he is positive in his statements If he says "That stiff arm of yours may possibly be of hysterical genesis and it s just possible that you might be able to move it but then again I may be mistaken" he will not get anywhere

What he must do is to say the minute he sees the arm held in a hysterical position "Why that s a typical case of a nervously weakened arm I have cured hundreds of them in a few minutes Your muscles and nerves are perfectly all right you ve just lost confidence in them See your fingers move a little If the nerves were gone you couldn t do that See also you can feel If the nerves were gone you couldn t do that Come now start moving the arm and in a few minutes you will be able to move it well Soon you will be all right"

Then the patient is likely to start moving the arm

What the Patient Can Do The patient often says "Well supposing I am nervous or a bit psychoneurotic what can I do to help myself?"

The first thing to do is to begin right away to learn to face difficult things and to tackle problems and to solve them quickly If a man lives sanely and thinks sanely he is likely to stay sane He must try also to live by one of Osler s wisest maxims which was to "live each day in day tight compartments worrying little about the morrow and wasting no regrets over the mistakes and sorrows of the past" Another of Osler s great bits of advice was to "burn your own smoke", to keep quiet about discomforts and not inflict

constant recitals of them on everyone who will listen

Many persons, if they set their minds to it, could get away from some of their difficult situations Many would be better if they could only make up their *minds what they* are going to do about their handicaps and frustrations Many a woman who is fretting and worrying herself into illness could get well if she would stop thinking only of her self and try to do things for her neighbors and her city Sometimes a man can get better if he finds a hobby that will keep him busy in his spare time

So many people get into trouble because they do everything hurriedly and with strain They should try to work without such feel ings of tension and hurry For instance, a bank teller admitted that he broke down and went to pieces whenever the line in front of his window got beyond a certain length I said to him "Why look at the line? Just look at the man at the window and attend to his business as if he were the only man in the bank"

Worry One of the greatest troubles of many persons is their tendency to worry foolishly Often of course, they have good reasons to be worried and then we physicians should not tell them airily to "forget it" If we were in their predicament we would worry, too But many a worrisome woman has not much to worry about, and we can then admonish her and urge her to mend her ways

Austen Riggs had good advice for worriers He said 'Note if the problem is yours to solve If it isn't, and you can t do anything about it, obviously you shouldn t worry about it"

For instance here is a woman who is worrying herself sick because her daughter does not get engaged to a certain man If she would only admit that the problem is not hers but the daughter's she might be able to stop worrying and go about her business

The next question for a worrier is If it is your problem can you tackle it and solve it now? If so then it ought to be tackled right away If it can not be tackled now, then wait until it comes up for solution Furthermore, if the problem is one that can and should be solved with the help of expert advice, then one should get it quickly, perhaps from a lawyer, a banker, or a physician

Finally, when the decision is made, the subject should be closed One of the great est troubles of many persons is that after *they have made* a decision, they keep re opening the matter again and again Far better is a poor decision quickly made and abided by than a better one not made, or if made, not adhered to I often remind a woman that I have to make big and impor tant decisions all day and quickly, without worrying about them Why should she not learn to make her small decisions about the home quickly and finally? It would save her much worry and fatigue and unhappiness

Often a woman frets herself into illness trying to make up her mind about a divorce I say to her, "Here is an imaginary button on the end of my desk, press it now and you'll be back from Reno with your decree in your hand"

If she refuses to press the imaginary button, I say, "There you are, you do not really wish to get that divorce or you are not tough enough to hurt others, or to face the world alone, so stop thinking about it and settle down to make a better go of your marriage'

Conflict with Others. Many persons are upset much of the time because they keep getting into needless arguments or fights with people about them Mothers are con stantly clashing with their children or with the husband, and these conflicts are tiring A more sensible or thoughtful or self con trolled person would probably never have started any of the rows She would not have told her boy not to go out to play when there was no good reason why he should not have gone To mothers I say, "Try never to start anything with your children unless you feel that it is very important to correct their be havior or to keep them from doing something that they much want to do"

So often when a child wants to go some where the mother says "No" and that starts a long argument and a clash of wills which leaves the woman tired and almost ill Usu ally her only reason for interfering with the child's plans was that she would worry until he or she came home

A kindly, friendly, courteous, tactful and sensible man can work for months with his

colleagues or employees without ever uttering a harsh word or getting into open conflicts He will mind his own business he will not bother other people and he will not try to take away their prerogatives He will always yield on nonessentials and will let the other fellow have his way whenever possible He will not try to run the lives of those about him If he ever has to correct an employee he will do it with kindness and tact and not before others

Childish Behavior Most of the troubles in the home and perhaps in the office are due to childish behavior Hence it is that every man and woman should strive to act always like a grown up

Much of a mother s annoyance and strain are due to the poor discipline of her children and this is usually her own fault If she never asked them to do anything unless there was a good reason for it and then if she saw to it that they obeyed quickly and courteously life would be much easier for the children as well as for her Too often the mother gives endless orders that are never obeyed and then after years of this she wonders why she is treated without respect If only mothers would not "start something when they have not the strength the pertinacity or the right on their side to carry it through

Excessive Shyness Many of the troubles of slightly psychopathic persons in this world are due to their shyness and self consciousness their feelings of inferiority and the strain of meeting their fellows With help from a wise physician some of this shyness can be overcome Many a shy young woman has been helped by being told by the physician that she with her good looks trim body good education and courteous ways has no reason to feel inferior Sometimes such feelings of inferiority have been built up by a jealous stepmother or a sadistic brother or an ignorant husband

On Getting Rest One of the most important things many a nervous person needs to do is to learn to get [illegible] sons putter around until midnight or later when they could easily be in bed or asleep by 10 o clock Many spend their Saturday afternoons and Sundays doing too much Any so called recreation which leaves a man or woman rested is good whereas anything that leaves him or her more tired and more nervous and tense is bad

It may take some argument to get a woman to try to rest She will feel that she will be a bad mother and a bad wife if she takes time out to rest I often tell such a woman that she who so wants to be a fine mother is being a poor one because she is too irritable to get along with her children With a few weeks of rest perhaps at a sister s she could be a new woman Occasionally when a woman is tired out and at the end of her rope a sort of Weir Mitchell cure in a sanatorium will do most good if it can be secured or afforded

Treatment with Drugs There is not much in the way of drug treatment for persons who are nervous and tired Many physicians give phenobarbital or bromides three times a day and sometimes this helps and gives some comfort but I dislike to start persons on such a habit It would seem better to have the patient take a sedative only [illegible] sleep he or she is likely to get better In my experience the use of barbiturates is not dangerous and no one who has any sense will ever become habituated to these drugs In 40 years I have never seen them produce enslaving habituation comparable to that which often follows the taking of opiates

There are quite a few persons who get to sleep easily enough at bedtime but who wake about 4 in the morning and then cannot drop off again I give those persons bromural because it is a quick acting drug and its effect is likely to be over in 2 or 3 hours Under these circumstances a person who has taken it can get up at 7 with a clear head

Treatment by Psychiatrists Only the patients with the worst neuroses or psychoses are likely to need the help of a psychiatrist or are likely to consent to go to one Needless to say psychiatrists could help many of our other nervous patients but there are not enough of these specialists to go around There are only a few thousand of them to care for the millions of the neurotic and psychopathic Obviously then nearly all of

the handling of nervous patients must be done by nonpsychiatric practitioners The *big problem today is to teach these physicians to recognize neuroses and psychoses when they see them*

Unfortunately many of the neurotic patients who cannot be helped by the nonpsychiatrically trained physician cannot be helped even by the psychiatrist They are the persons with a low intelligence quotient marked hypochondriasis marked depression a tendency toward schizophrenia, or a psychopathic personality which gets them into one scrape after another Most of the persons with a psychopathic personality are too self centered and selfish ever to be reached by any type of therapy Others do well when *sheltered and kept away from a troublous* world but, when they go back home to strains and annoyances and too much alcohol they break down

The wise and experienced physician can *usually tell within a few minutes the type of* patient he can help and the one he cannot Usually he can learn most about the serious*ness of a patient's mental situation by talk*ing to the spouse and other long suffering members of the family They alone may tell of insane, antisocial or unreasonable behavior, terrible wastage of the financial resources of the relatives alcoholic sprees disgraceful sexual episodes or violent outbreaks of temper Many a time I have seen a person of this psychopathic type who had spent years in the hands of surgeons and others getting operated on and treated for this and that. If one of these physicians had ever interviewed the family and got them to talk freely he would have been astounded to learn that his patient was insane

WALTER C ALVAREZ

CEREBRAL EMBOLISM THROMBOSIS AND HEMORRHAGE INCLUDING CEREBRAL ARTERIOSCLEROSIS

The treatment of the manifestations of any one of these three cerebral circulatory disturbances requires first of all their diagnostic differentiation Aring and Merritt's clinical and pathologic study as well as many other contributions to the literature have been devoted to this task but the fact remains that the differential diagnosis is not always feasible Embolism is usually diagnosed in younger individuals with evidence of heart disease, mostly rheumatic often with evidence of other embolic lesions in the retinal arteries or elsewhere in the body Yet many arteriosclerotics, with or without

of little diagnostic value since each may be affected by cerebral edema reflectory changes in the cerebral circulation or, nat

accompanied by loss of consciousness In doubtful cases, a history of essential hyper*tension will suggest cerebral hemorrhage* Blood in the spinal fluid is occasionally present in massive hemorrhage when the inter*cerebral hemorrhage has perforated into the* ventricular system or into the intra arachnoid space Increase of spinal fluid pressure *over 160 mm of water is often seen in* cerebral hemorrhage The complicating subarachnoid hemorrhage betrays itself fre*quently by rigidity of the neck and leukocy*tosis in the blood may be seen as a reaction to the hemorrhage

*Some of the neurologic findings in circula*tory brain lesions are helpful in differential diagnosis Thrombosis, seldom embolic encephalomalacia is often localized in the posterior parts of the brain irrigated by the a cerebri posterior, and produces hemianopsia without hemiplegia *Hemorrhages rarely* occur in this area -Evidence of circulatory lesions in the brain stem, cerebellum and circumscribed cortical areas (*persisting* aphasia monoplegias), as well as of multiple brain lesions indicates ischemia, mostly of thrombotic origin *Hemorrhages in the cere*bellum are rare Wilson gives their percentage as about 0 1 per cent of brain hemorrhages Signs of cerebral irritation *in the* form of epileptic seizures are usually found in ischemic cortical lesions and in cerebral arteriosclerosis (mostly in *hypertensive pa*tients) but also may be found in embolism

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a perforating hemorrhage accumulates over the cortex or seeps into the ventricles In the latter case decerebrate rigidity and tonic extensor fits are often seen

The course and prognosis of the three cerebral vascular lesions are in general somewhat different although here again the individual case may not correspond to the rule Cerebral embolism and thrombosis have a smaller mortality percentage (about 50 and 30 per cent respectively) whereas massive hemorrhages are fatal in almost 80 per cent In embolism the initial loss of consciousness may be overcome within a few days but in massive hemorrhage a deepen

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ness A fatal course in cerebral thrombosis owing to the gradually increasing encephalomalacia or to a complicating circulatory failure or to bronchopneumonia seldom leads to death under a week s time and the patient s fate may remain precarious for a month Many patients with cerebral arteriosclerosis suffer in their lifetime from multiple ischemic lesions which by no means always appear clinically as "strokes Textbooks on neurology and psychiatry describe a variety of syndromes that may occur in cerebral arteriosclerosis

The *clinical pathology* of circulatory brain lesions consists of an effusion of blood through damaged vessel walls in patients suffering from essential hypertension in a so called massive brain hemorrhage and of an ischemia of the brain in patients suffering from arterial embolism or from an arteriosclerotic encephalopathy In many instances the effects of arteriosclerotic and degenerative weakening of the vessel walls in hypertension (described as hyalinosis) are combined Therefore a hypertensive patient often suffers from multiple ischemic brain lesions before a massive hemorrhage occurs Treatment ought to consider that extreme variations of blood pressure in the earlier stages of

is of more ominous significance than the high systolic pressure Increased systolic pressure without rise of diastolic pressure, as often seen in old arteriosclerotics or in certain aortic lesions rarely precipitates a brain hemorrhage On the other hand cerebral ischemia in arteriosclerosis often follows a drop in blood pressure which explains the frequency with which such patients suffer strokes during the night or under the effect of heart failure In fact encephalomalacia in cerebral arteriosclerosis is by no means always caused by a visible arterial thrombosis as many pathologists have found but is often the effect of tissue anoxia in areas of the brain insufficiently irrigated in the presence of arteriosclerotic narrowing of the vessel lumen particularly at the sites of the branching off of the smaller arteries from the large basilar vessels

Much has been written about arterial spasms contributing to cerebral damage in the hypertensive and arteriosclerotic group of vascular brain lesions One may safely assume that a certain number of transient

in hypertensive patients may be caused by vascular spasms This belief arises from the success of antispasmodics in some of these cases Their effect is usually of a prophylactic character because the purely functional contraction of an artery is of short duration only and the longer lasting impairment of brain function is probably due to postspastic tissue edema Apparently transitory brain lesions of days or weeks' duration so frequently seen in hypertensive or arteriosclerotic patients should be accepted as evidence of organic tissue damage mostly small ischemic foci the occurrence of which betrays organic vascular damage and not a purely functional vascular spasm The importance of vascular spasms appears to be much greater in the extensive cerebral ischemia that follows arterial embolism Here a reactive spastic contraction of the suddenly embolized artery is combined with functional disturbances of the arterial and venous blood flow over a wide area leading first to cerebral edema and finally to ischemia with softening of the brain tissue

The early or prophylactic treatment of circulatory brain disturbances is the more desirable since any severe type of vascular damage will show itself in the impairment or loss of certain cerebral functions, which

in time may become compensated to a variable degree but can never be cured

Prophylaxis of Cerebral Hemorrhage The ideal solution to this difficult problem is to stop the fateful progress of the arterial hypertension By what means this can best be achieved is discussed elsewhere in this book Thoracolumbar sympathectomy will often have to be considered and every experienced physician knows how difficult a decision this is in view of the fact that lasting results can never be predicted It may be interesting to know that surgeons such as M M Peet and J L Poppen do not regard cerebrovascular accidents as contraindications in themselves although Peet requires his patients preferably under 50 years of age to have recovered completely from their vascular lesions American as well as European surgeons have reported a goodly number of patients with cerebrovascular accidents before sympathectomy with recurrences in only about 10 per cent That patients occasionally suffer strokes during a sympathectomy indicates the necessity of evaluating the severity of true arteriosclerotic lesions of the cerebral arteries This may be facilitated by roentgenographic study of the skull and by arteriography Indirectly one may conclude that coronary sclerosis particularly in hypertensives is frequently associated with cerebral arteriosclerosis It is not surprising that this group of cases with early ischemic lesions in heart and brain succumbs to the rapid lowering of the blood pressure after sympathectomy The state of the retinal arteries and the degree [illegible] form about [illegible] of the [illegible] help to decide whether or not sympathectomy is indicated One may agree with R S Palmer that sympathectomy is the treatment of choice for patients with malignant hypertension in the presence of retinopathy with papilledema after dietary and medical treatment have failed to improve the condition Like Poppen and Lemmon we feel especially that cases classified as grade IV retinopathy with choking of the optic disks and retinal hemorrhages occurring in relatively young patients and with a fulminating or rapidly progressing hypertension demand immediate operative intervention Even grade IV retinopathy may disappear and not return for some time after sympathectomy As Peet has stated it is a fact that malignant hypertension with grade IV neuroretinopathy predicts an extremely serious course of the disease often terminating in massive cerebral hemorrhage an event which at least in a certain number of selected cases can be prevented or postponed by dorsolumbar sympathectomy On the other hand one should bear in mind also that milder cases of arterial hypertension with grade I or II neuroretinopathy and with no stabilization of high blood pressure may succumb to a cerebral hemorrhage It is here where the clinical picture before the hemorrhage does not appear to be threatening that the decision in favor of a sympathectomy will be particularly difficult We think that it should be postponed until all other therapeutic measures have been exhausted

Venesection for the prevention of cerebral hemorrhage has been generally abandoned and as it seems to this author not quite justly Particularly in hypertension with polycythemia it should be considered Edwards and Bordenave found that the removal of 500 cc of blood was followed by a fall in blood pressure lasting for about 2 months and accompanied by an improvement in the subjective symptoms (see also below)

Short transient pareses and paralyses in patients with arterial hypertension (and occasionally in those without) may be prevented or more rapidly overcome by vasodilating drugs Papaverine may be given intravenously if rapid action is desired in doses of 0 03 to 0 06 gm By mouth 0 1 gm three times a day is the minimal effective dose Its low toxicity permits even higher doses One may combine papaverine with 30 mg of phenobarbital or aminophylline The latter injected slowly can also be given intravenously in doses of from 0 3 to 0 5 gm

Treatment It is extremely important to recognize the early symptoms of circulatory insufficiency of the brain In many instances the initial stage shows a clinical syndrome which is best described by the term "pseudo-neurasthenia" The diminution of mental alertness the impairment of energy concen

tional tension, hypochondria, depression, etc —all these manifestations which may or may not terminate in the picture of an arteriosclerotic dementia reveal themselves often before neurologic signs of a cerebral circulatory decompensation make their appearance. Classical symptoms and signs of the latter include headache, sometimes combined with paresthetic sensations in the chest, abdomen, or extremities, an occasional feeling of dizziness, sometimes of true vertigo often with slight impairment of hearing, fainting spells, disturbance of sleep, and the various focal motor or sensory pareses including speech and other disorders which follow the many ischemic (less frequently the hemorrhagic) lesions of the brain.

Patients with early signs of cerebral arteriosclerosis or those in the presclerotic phase of hypertension often respond well to the common sense laws of mental and physical hygiene—reduction of activities, interpolation of rest periods such as one hour of bed rest after lunch, periodic vacations, lessening of responsibilities, regular and moderate dietary habits, and avoidance of exhaustion. Although the noxious effect of nicotine in arteriosclerosis is debated, the extent to which smoking may contribute to the causation of certain symptoms, particularly those of headache and dizziness, should be investigated. If the discontinuance of smoking brings about disappearance or mitigation of symptoms, then complete abstinence from nicotine should be recommended. Alcohol, too, is often poorly tolerated by these patients and, if taken at all, should be consumed only in great moderation. Dietary measures should be directed against so-called heavy and highly spiced food, and should provide for light meals especially at night, since overloading of the intestinal tract favors brain anemia. Overweight is another condition often associated with premature arteriosclerosis, and intelligent gradual reduction of obesity often has a beneficial effect.

HEADACHE. The treatment of recurrent headaches of arteriosclerotic and hypertensive patients is often a problem although many patients take these headaches lightly since they show a spontaneous tendency to disappear once the patient is out of bed and has put cold water on his face. These headaches may be subdivided into a temporofrontal pain, with all the characteristics of a migraine, and a severe ache in the nape of the neck radiating over the occiput up to the vertex and downward over the shoulders. Patients with the latter type often complain of an unpleasant sensation which they describe as that of a tight band or cap around the head, as if the head were in a vise.

As the result of a dilatation and a distention of branches of the external carotid artery, the temporal as well as the middle meningeal arteries, the frontotemporal pain corresponds, to all appearances, to the true migrainous headache. Yet, only about half

these headaches become more frequent. However, there is no parallel between the fluctuations of the blood pressure and the headache, and quite a few patients lose these headaches with mounting pressure, especially after the occurrence of vascular brain lesions. Wolff's explanation of these headaches as the combined effect of stress, fatigue and other conditions leading to a decrease in vascular tone and distention plus the dilatating effect of increased blood pressure is borne out by everyday observations. Treatment of these headaches should consist first of all in having the patient avoid all possible situations which might affect unfavorably the contractile state of his arteries. This is most important, since the painful condition of the branches of the external carotid artery is probably accompanied by undesirable and ultimately harmful tonus changes in the cerebral arteries. Even more important than the medical management are those therapeutic measures dealing with the patient's way of living and working as well as with his emotional attitudes, his frustrations, his maladjustments, and often with present neurotic

these patients have already been mentioned. The psychologic problems of these patients can well be left to the patient understanding and wise counselling of the general practitioner, except where the personality conflict

is such as to indicate more intensive treatment by a psychiatrist All of us have seen many arteriosclerotic and hypertensive patients lose their migrainous headaches with a change of certain detrimental habits with the instituting of a more wholesome life and with the overcoming of their neurotic ways of dealing with their problems

The medical treatment of these migraine like headaches follows the same principles outlined in the chapter on migraine with the difference that ergotamine tartrate may be used only if the patient is not suffering from marked organic changes of the arteries The same holds true for all those agents which like ephedrine benzedrine epinephrine and pituitrin have a constricting effect on blood vessels but at the same time increase systemic pressure Only caffeine 0 3 to 0 6 gm given by mouth or as a cup of strong hot coffee may be used although while some patients feel relieved by it others feel worse Of all the agents which act by raising the pain threshold acetyl salicylic acid (0 5 to 2 0 gm in tablets) or if necessary codeine phosphate (0 06 gm) are most satisfactory To prevent these headaches after a hectic day with its numerous strains or after a prolonged evening with its overstimulation satisfactory general relaxation and sounder sleep may be gained with 0 1 gm of phenobarbital 0 2 gm of sodium amytal or 0 1 gm of nembutal Also a combination with 0 5 to 1 0 gm of aspirin may be tried Many patients with cerebral arteriosclerosis show symptoms of mild depression associated with anxiety particularly after strenuous mental activities and these individuals benefit from taking 0 06 to 0 1 gm of powdered opium in capsules at bed time only or if necessary two or three times during the day after meals The danger of addiction is negligible

The occipital and skull pain with or without temporofrontal headache may be a harmless muscular pain due to spastic muscular contraction (see the chapter on Headache where the treatment of these pains is discussed) When associated with migrainous headache it frequently reacts to the medication just described Many of these patients who complain of occipital headaches when resting on a feather pillow are relieved when change is made to a horsehair pillow Occurring in arteriosclerotics without hypertension during the early morning hours or with mental fatigue the pain may be due to a certain degree of brain anoxia possibly combined with increase of venous pressure Improvement of cerebral circulation can be achieved by avoidance of strain and by mild physical exercise General recommendations such as these should be complemented by a more specific support of the general circulation when necessary

In the final stages of malignant hypertension for the most part those with renal failure and stage IV retinopathy another type of headache may occur more lasting not limited to the morning hours and often associated with nausea and vomiting These headaches are seen in patients with so much evidence of organic vascular damage that with or without evidence of focal brain lesions their causation by a hypertensive encephalopathy must be assumed This condition not rarely complicated by epileptic seizures shares with the so called hypertensive crises the occurrence of vascular spasms or organic ischemic cerebral conditions followed by edema of the brain Renal insufficiency with azotemia may or may not complicate this condition The often severe headache reacts to a lowering of the generally increased intracranial pressure Repeated spinal punctures (at least 20 cc) have proved helpful in a number of cases as has also the intravenous infusion of hypertonic solutions (see below) Dietary measures especially a low sodium diet are recommended

Prevention of Cerebral Embolism The prophylaxis of embolic brain lesions concurs with the prevention of thrombus formation as the source of emboli e g with the successful management of a rheumatic heart the most frequent source of embolism particularly in younger persons This and the use of anti coagulants (dicumarol and heparin) in thrombus formation are described elsewhere

The treatment of apoplexia or what is generally understood as a stroke is usually regarded as symptomatic Yet the degree of recovery of many a hemiplegic depends on the medical attention and nursing care given to these patients In addition it is possible

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[illegible]

injection of a 1 per cent solution of procaine hydrochloride (without epinephrine) a dermal wheal is placed over the tip of the seventh transverse process then a 4 inch (9 cm) 22 gauge needle is inserted through this wheal It must shortly make contact with the tip of the transverse process, which is quite superficial Then the needle slides along the superior border of the transverse process until it contacts the body of the sixth cervical vertebra Aspiration is now made for air bubbles for blood for spinal fluid, and if none of these is observed 10 cc of a 1 per cent solution of procaine hydrochloride is injected aspirations being made repeatedly during this procedure

A successful block is followed within 10 to 15 minutes by Horner's syndrome by dilatation of the conjunctival vessels, by dryness and in creased warmth of the face and ear lobes on the side of injection and by rising temperature and dryness of the corresponding upper extrem ity If Horn[illegible]

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The results of stellate blocks are more en couraging in embolism than in thrombosis and better in younger than in old patients The latter observation can well be explained by the defective brain tissue regulation of the capillary blood flow in the presence of severe cerebral arteriosclerosis The block should be performed shortly after the stroke, possibly within the first 24 hours Yet even after days or a few weeks some clinical im provement can be obtained The block may be repeated daily or after longer intervals so long as a beneficial effect is observed as well as in cases of repeated cerebral insults The risk involved is so little that the recom mendation of Amyes and Perry to make the stellate block a "routine treatment by well trained persons for acute cerebral thrombo sis or embolism" deserves serious considera tion Patients suffering from more or less transient cerebral palsies indicating increas ing localized ischemic disturbances may oc casionally benefit from a stellate block as a preventive measure, to counteract the narrowing of an artery by improving the collateral and capillary circulation A simul taneous bilateral block is said to be danger ous, and Amyes and Perry recommend wait ing at least 4 hours between blocks

Wernicke has already suggested the surgi cal removal of blood clots after massive hemorrhage, and many of us, likewise, have thought of saving a patient from the effect of a hemorrhage by removing the blood Ever so often favorable reports of such a procedure appear e g, W B Hamby's series of 16 surgically treated cases, with 14 re coveries Surgery is considered in cases with apoplectic or with gradual onset, where there

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A successful block is followed within 10 to 15 minutes by Horner's syndrome, by dilatation of the conjunctival vessels, by dryness and increased warmth of the face and ear lobes on the side of injection, and by rising temperature and dryness of the corresponding upper extremity If Horner's syndrome does not develop the injection must be regarded as faulty and should be repeated If improvement is to follow cervical sympathetic block it should be noticed within the next 10 minutes, the improvement may then continue

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is a progression of signs and development of evidence of increased intracranial pressure As a procedure less drastic than craniotomy, trephine aspiration of the clot has been recommended but, of course, aspiration does not eliminate the solid clots present in most hematomas Contraindications to surgical removal of the hematoma include not only the usually poor condition of the patients with massive brain hemorrhage, but more especially the fact that almost every otherwise fatal hemorrhage does its damage, i e, destroys brain tissue in the initial phase, usually leading to an interruption of the pyramidal tracts in the internal capsule, and therefore to an irreparable complete hemiplegia Loss of brain function through pressure of the hematoma without serious tissue destruction will generally clear up spontaneously Removal of blood clots distending the aqueduct and the fourth ventricle and producing a fatal compression of the medulla (Cheyne Stokes breathing and respiratory paralysis) has also been recommended, and occasionally executed with success Most of these hemorrhages stem from a primary hemorrhage in the basal ganglia Again, the patient may survive but may remain hemiplegic

General Treatment Treatment of increased intracranial pressure is important in all types of strokes, although its mechanism —whether of edema in embolism and thrombosis, or of brain volume increased by a large hematoma—may necessarily vary In all three, spinal puncture is employed, but its advisability is doubtful except under the conditions described previously Large encephalomalacias do not profit from the puncture and cerebral hemorrhages may benefit temporarily in the rare instances where there is an accumulation of large amounts of blood within the subarachnoid space Lowering of the intracranial pressure in hemorrhages may be helped by the deviation of the arterial blood from the head to the abdomen and lower extremities by means of the almost ritualistic use of the ice bag on the elevated head and of hot applications on the abdomen and legs Another agency is venesection Almost forgotten in modern medicine, this old and discredited remedy deserves to be tried in plethoric cases of arterial hypertension with facial cyanosis, venous congestion in the neck, and full, pounding pulse Not more than 300 to 400 cc of blood should be slowly removed and the patient should be closely watched for any alarming symptoms It must be thoroughly understood that bleeding is definitely contraindicated in encephalomalacia, which again shows the importance of the differential diagnosis High blood pressure may follow sudden extensive encephalomalacia and this transient reaction must be recognized as such Care should be taken to protect these patients from all exertion and emotional strain which might raise the blood and intracranial pressure, they should not be moved unnecessarily, should be kept quiet, and should not receive disturbing visitors

Cerebral edema, particularly that accompanying encephalomalacia may be combated with hypertonic solutions intravenously From 30 to 50 per cent dextrose or, better, 50 per cent sucrose, solution is usually given in amounts up to 200 cc and more (A 25 per cent dry serum albumin solution would be better, but it is expensive) Aminophylline (0 3 to 0 5 gm), which seems to lower the spinal fluid pressure, may be added to the infusion which must be administered slowly (100 cc within about a quarter of an hour) Emptying the bowels with the use of 60 cc of saturated solution of magnesium sulfate helps the process of dehydration

Support of the cerebral circulation is particularly necessary in arteriosclerotic encephalopathy in cases with poor general circulation and heart failure Oxygen administration through a nasal catheter aids the general circulation and overcomes anoxia, in itself an important factor in the high mortality rate Care taken to promote unobstructed pulmonary ventilation serves the same purpose The patient should be placed on his side to permit free excretion of saliva and to prevent the tongue from falling back Accumulating mucus should be aspirated through a catheter or with the help of an aspirator

Against restlessness the different barbiturates are helpful, and, if necessary, may be given intramuscularly or intravenously Chloral hydrate is an especially good sedative in states of agitation, but has a tendency to lower the blood pressure It can be given by mouth or rectum in amounts up to 3 gm

daily Narcotics should be avoided for they have a depressing effect on the respiratory center and increase the intracranial pressure

Nutrition becomes a problem when after 2 or 3 days patients are still unconscious or unable to swallow Tube feeding will then be necessary Fluids should be withheld in cases where active dehydration is being attempted but not for longer than 1 or 2 days During the first 3 days 2000 cc of fluid intravenously is usually sufficient Once the paralyzed patient has survived the first week nursing care becomes of decisive importance The skin must be protected against the development of bedsores Much can be done by handling the patient carefully by shifting his weight from time to time by avoiding wrinkles of the bed sheets by using air or better water cushions by inserting cotton rolls or pillows by watching carefully such places as the buttocks heels etc by keeping the patient clean by gently rubbing the skin with 50 per cent alcohol and then powdering it with talcum Both mattress and patient must be protected against urine and feces Diapers absorbent material with oakum special mattresses and urinals have their place Bedsores may be treated with scarlet red ointment (not too long) cod liver oil ointment or balsam of Peru with castor oil in equal parts Deep penetrating skin ulcers may have to be treated surgically with better chances for success now that the local and general use of penicillin has been accepted Hot water bottles must be applied carefully to avoid burns The bowels can be better regulated by enemas (with water containing small amounts of sodium bicarbonate) than with cathartics In case the spontaneous emptying of the bladder is disturbed catheterization at 6 hour intervals under aseptic conditions is necessary

Complete rest should be maintained for about 2 weeks when the period of re education may begin The final outcome of many a severe paralysis depends on how paralyzed extremities have been handled during the many months of slow return of function Regular passive later active movements prevent painful joints and ankylosis and combined with massage they prepare the paralyzed limb for the gradual return of innervation Tendency to contractures appears soon and must be counteracted by favoring the very opposite positions e g passive dorsiflexion of the foot by means of a wooden board or box flexion of the knee with the help of a pillow support of the extensors of the fingers and wrist and the supinators and adductors of the upper arm Active exercise is often facilitated at least at first in a warm bath which, at the same time has a soothing effect on painful and disturbing spasms These involuntary contractions of muscle groups or of a whole extremity are often difficult to treat Massive sedation may help heat should be tried taking care to avoid skin irritation and occasionally light massage eases them (The use of curare in the form of d tubocurarine chloride 3 per cent suspension in 4 8 per cent wax and peanut oil is not without danger) As the patient gradually learns to move his extremities again special attention should be given to the re education of purposeful synergic muscle action such as that needed in walking in reaching for seizing and holding objects in dressing in writing etc The more systematically gymnastic exercises and other forms of physiotherapy are used by hemiplegics the better the results The reader may profitably study the article by E W Lowman with its numerous references pertaining to this subject

Contractures which may develop in spite of all precautions and treatment can in selected cases be improved by orthopedic surgery Speech training for aphasic patients necessitates personal experience with the problem and should not be delayed Improvement of paralysis following vascular accidents may continue for 2 to 3 years

Many patients with cerebral arteriosclerosis with or without hypertension—sometimes following strokes but also in the progressive course of cerebral arteriosclerosis toward arteriosclerotic dementia—become therapeutic problems because of their disturbances of sleep restlessness agitation confusion and depression It is generally recognized that the use of barbiturates and bromides does not have desirable effects On the contrary they contribute only too often to increasing confusion disorientation and agitation The different xanthines are more successful here Theobromine calcium sal

icylate (theocalcin), 0 5 gm three times daily, or theophylline ethylenediamine (aminophylline), 0 1 to 0 2 gm three times daily by mouth is recommended The use of a few cups of strong coffee during the day has often a surprisingly good effect in non hypertensive cerebral arteriosclerosis Faint ing spells particularly when combined with retrograde amnesia and convulsive phenomena usually respond well to dilantin (*diphenylhydantoin sodium*) *although these* patients will have to be watched carefully for toxic symptoms (More information will be found in the article on Epilepsy) Fainting *spells with dizziness* or even with true vertigo and then usually combined with tinnitus and diminution of hearing point to *ischemic conditions in the vestibular system* and the inner ear, possibly on the basis of a sclerosis of the a auditiva Such patients may react well to nicotinic acid by mouth in amounts large enough to cause a sensation of warmth in the head When these attacks of vertigo resemble a Meniere syndrome, papaverine 0 1 gm twice or three times daily (also combined with quinine sulfate 0 1 to 0 2 gm) should be tried (For more details see under Migraine)

Dizziness associated with a disturbance of equilibrium pointing to a cerebellar disturb ance is often very resistant to treatment Again, vasodilators, such as nicotinic acid or nicotinamide may be tried Here, as in other manifestations of cerebral arteriosclerosis, iodine has been used by many experienced physicians, although the rationale of this medication is rather obscure One may give it by mouth as potassium iodide, 0 3 gm three to five times daily after meals in the form of enteric coated pills In progres sive forms of cerebral arteriosclerosis the administration of sodium iodide intravenously in doses of 2 gm every other day for several weeks, followed by potassium iodide given orally for a few months is recom *mended One should* watch for signs of iodide intoxication, particularly in patients with hyperthyroid manifestations Arterio sclerotic parkinsonism is treated in much the *same manner as paralysis* agitans, hyoscine hydrobromide (0 0005 gm three times daily) being the most frequently used drug The acute bulbar paralyses on an arterio sclerotic *basis often create* therapeutic problems, because of the patient's inability to swallow (dysphagia) Tube feeding as described *elsewhere in this book is indicated* in these cases

A general recommendation may conclude this chapter on treatment of cerebral arterio *sclerosis Although this condition should* be regarded in general as a progressive disease, leading to irreversible brain tissue damage, everyday experience testifies to the fact that wise *management of these patients is often* followed by a slowing down or apparent standstill of the disease process over long periods of time A nihilistic attitude based on therapeutic pessimism is not justifiable except in advanced cases of physical and mental disability

Frederick Hiller

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SUBARACHNOID HEMORRHAGE

To treat successfully a hemorrhage in the subarachnoid space of the brain, one should know the source of the hemorrhage Evi dence of a grossly bloody spinal fluid is com mon to subarachnoid hemorrhages of dif ferent origin In general one distinguishes between a spontaneous subarachnoid hemor rhage, which some understand to be "non traumatic," others as "without obvious cause," and a secondary subarachnoid hemor

rhage, i e, secondary to a primary intracerebral hemorrhage It is obvious that such a distinction is, to say the least, unscientific All of these hemorrhages have a cause, and this should be ascertained, if possible, in each individual case as an essential part of the diagnosis and treatment

Acute Massive Subarachnoid Hemorrhage Treatment has, up to the present time, remained conservative Lately, this lack of therapeutic activity has been challenged by neurosurgeons whose criticism (Wechsler and Gross) appears vindicated already by the fact that almost 40 per cent of these patients die in their first attack The death rate in second attacks climbs up to 70 per cent or more Spinal puncture has been used in subarachnoid hemorrhage not only as a diagnostic but also as a therapeutic procedure However, serious doubts are expressed as to the advisability of repeated even daily, punctures as recommended and practiced Those who have seen many cases of subarachnoid hemorrhage will agree that the first diagnostic puncture, whereby small amounts, 5 to 10 cc of bloody fluid are slowly removed, may be followed by a slight, though usually transient amelioration of the general reaction of the brain to the sudden increase of intracranial pressure caused by the bleeding But there can be no doubt that during the early stages of the hemorrhage, the increased intracranial pressure occasioned by the extravasation frequently has a protective value in tending to reduce the rate of leakage and so promote coagulation We agree with Symonds when he concludes that "the indications for therapeutic puncture are the signs of a dangerous increase of intracranial pressure, especially if these be progressing .. In such circumstances the risk of death from compression outweighs that of the operation itself" Repeated punctures which may easily upset the hydrodynamics in the subarachnoid space and even tually cause a new hemorrhage should be avoided, unless deepening coma, increasing pulse and blood pressure, fresh bleeding and depressed respiration endanger the patient's life

If, in the presence of an acute subarachnoid hemorrhage, serious doubt exists as to its source and the question of surgical exposure arises, arteriography is indicated The use of "diodrast" (iodopyracet) has made angiography a relatively safe procedure, which may be used in the acute as well as in the subacute stages of the hemorrhage (Wechsler and Gross). If, by this means, a vascular malformation or a tumor in an accessible area of the brain, usually over the cortex, is verified, the treatment of choice will be surgical and the neurosurgeon should decide whether or not the tumor should be exposed If an operation does not seem feasible, roentgen treatment may prevent future hemorrhages

In cases of acute subarachnoid hemorrhage without a history suggestive of vascular malformation or tumor, and without the suspicion of a pachymeningitis, or of a traumatic, toxic, dyscrasic, or infectious hemorrhage, *in other words, in a case of most* probable aneurysmal subarachnoid hemorrhage, arteriography for localization of the aneurysm and for possible surgical management of the case must be considered by the responsible physician Whether one decides on an arteriogram or not depends, first, on what one has decided to do in case an aneurysm is found, and, second, on the patient's condition (continued bleeding, deepening coma, etc), and also on whether one is dealing with a first or with a repeated hemorrhage

An arteriogram for the visualization of the aneurysm is indicated in cases which enter the hospital in a second or in an even more frequently repeated attack These patients have only half as good a chance to survive as those suffering from a first hemorrhage An arteriogram is also desirable in cases, even without repeated hemorrhages, which show neurologic signs of increasing local pressure, probably due to an enlarging aneurysm

The surgical treatment of aneurysm, as performed by Dandy and others, shows by its high mortality rate (over 50 per cent) that, at least with the present technic, it cannot be recommended generally in first attacks of subarachnoid hemorrhage, with the possible exception of cases which show the ominous signs of continued or repeated bleeding

Ligation of the common carotid which reduces the blood circulation of the ipsilateral side of the brain about 50 per cent

and is less dangerous than ligation of the internal carotid will certainly not cure an aneurysm at the base of the brain but it may stop the bleeding and favor the thrombotic occlusion of a ruptured aneurysmal sac It will not have any marked effect on the tumor signs of an aneurysm Its usefulness is well established in arteriovenous aneurysms with pulsating exophthalmos which lie outside our discussion and it may be recommended in acute subarachnoid hemorrhage particularly when the first hemorrhage threatens the patient s life or in any case of repeated hemorrhage in younger individuals Wechsler and Gross do not see any danger in this procedure although the American and European literature contains reports of usually transient hemiplegias and brain damage demonstrated in ventriculograms after common carotid ligation Ligature has the advantage over direct surgical approach in aneurysm in that it is technically simple and its risks are slight compared with those of the other operation The ligature must of course be preceded by an arteriogram in order to ascertain the site of the bleeding branch of the internal carotid

Operative procedures present a still more difficult problem when patients ask advice one or more months after the acute signs of a subarachnoid hemorrhage have subsided Here H G Wolff s suggestion can be accepted that arteriograms should be made in the presence of significant symptoms referable to a probable aneurysm such as motility and sensory disturbances pointing to a localized intracranial mass Yet we think craniotomy and even ligature of the common carotid should depend on the clinical course One should not be too pessimistic as to the danger of brain tissue damage (hemiparesis aphasia mental disturbances etc) once the patient has survived his first acute attack In most instances these conditions improve gradually and often leave only small functional defects One will be more reluctant in recommending a carotid ligature on the left side (in a right handed person) than on the right and one should always consider the general brain condition which does not always correspond to the age of the patient

General Management The general management of an acute subarachnoid hemorrhage often has to deal with considerable agitation restlessness and excitement in the patient a condition that is anything but conducive to cessation of the bleeding Paraldehyde 30 to 60 cc per rectum barbiturates, intramuscularly or intravenously (e g sodium amytal 0 3 to 0 5 gm) will usually quiet the patient If headaches or pain along the spine (and sometimes also in the lower extremities) make the patient suffer and contribute to his restlessness codeine sulfate (0 06 gm) or demerol (100 mg) subcutaneously is recommended Morphine in the presence of cerebral respiratory impairment is dangerous Magnesium sulfate 300 cc of 25 per cent may be given by Murphy drip at a rate of 1 drop per second Increased intracranial pressure may be counteracted by the intravenous infusion of hypertonic solutions In addition the rules of conscientious nursing care should be followed as outlined in the treatment of apoplexia Patients should be kept in bed 4 to 6 weeks after the bleeding has ceased

As to the further medical supervision of these patients particular attention should be given to any disturbances of cerebral function and to the blood pressure In a large series of cases of subarachnoid hemorrhage reported by W B Hamby and others arterial hypertension was "the only constitutional disorder that occurred with sufficient frequency to be regarded as more than incidental" From such observations as well as from the prevalence of migraine in these patients one may conclude that patients who have suffered a subarachnoid hemorrhage should be checked and treated for abnormal variations of blood pressure and that their way of living ought to be so well regulated as to protect them against headaches which because of a concomitant dilatation and distention of the intracranial arteries may precipitate new hemorrhages

The treatment of subarachnoid hemorrhage of other etiologies must rest first of all on the approach to the underlying pathology It will be surgical in the presence of certain traumatic types such as primary subdural hematomas and hemorrhagic pachymeningitis It will be medical in the various types of blood diseases and dyscrasias as well as in infectious or toxic conditions

Frederick Hiller

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HEADACHE

The physician who has to treat a patient suffering from headaches especially those of a chronic recurrent or alarming type is confronted with the necessity of understanding the etiology or the mechanism of the head ache in question Harold G Wolff s work *Headache and Other Head Pain* the first systematic approach to clarification of the pathophysiology of the various types of head ache is recommended to all those who desire a more detailed account than this chapter can give them

Migraine The classical attacks of migraine headaches characterized by their periodic occurrence usually but not always by their unilateral frontotemporal distribution their prodromal sensations and cerebral manifestations are generally explained as the result of primary intracranial and extracranial vasospasms followed by the painful dilatation and distention of branches of the external carotid artery The premonitory sensations due to vasospasm are for the most part visual such as scintillations scotomas and hemianopsias but they may also include both sensory and motor disturbances of hemi lateral distribution and speech disorders Like epilepsy to which it has some relation (Lennox) migraine may betray itself in equivalent periodic emotional or mood disturbances and even mild twilight states Or with or without headache it may exhibit somatic phenomena of a painful character in different parts of the body and extremities as well as nonpainful intestinal disturbances metabolic upsets water retention fever etc All migrainous phenomena varying from case to case can be linked to different causative or merely precipitating factors which like allergies endocrine activities or disorders and frequently psychogenic or personality disturbances have to be well understood

The treatment of migraine though mostly concerned with the headache will be the more successful if the pathogenetic peculiarities of the individual case are understood and if therapy of the painful distention of extracranial or meningeal arteries is then supplemented by consideration of the pre headache phase and of the underlying causes

The simplest way to relieve or even stop the usual temporal headache is to reduce the blood flow into the distended palpably pulsating arteries by digital compression A few patients feel immediate relief with pressure on the temple others with pressure on the common carotid A tight wide rubber band around the head cold compresses and any other measures which will diminish blood flow are of value as well as procedures to lower general arterial pressure such as a warm bath followed by bed rest

If given early enough ergotamine tartrate in use for more than 20 years has proved to be effective in the majority of migrainous headaches However it is of practically no value if the headache has lasted for many hours and if organic though reversible edematous thickening of the palpable arteries has taken place But if given early and in a sufficient dosage its damping effect on the excessive pulsation of the extracranial arteries as the temporal artery for instance is visible and the headaches often subside with

is desired the same dose may be administered intravenously As an alternative ergotamine by mouth taken sublingually is recommended As soon as possible after the beginning of the headache a dose of 3 to 4

should remain under the control of the

physician and should not be given more often than once a week Furthermore advanced hypertension and cardiovascular disease must be regarded as contraindications to this treatment Should the patient show hypersensitivity to ergotamine such as nausea vomiting paresthesias muscle and chest pain and prostration lasting for more than 24 hours further use of the drug may be hazardous As an antidote atropine sulfate 0 5 mg subcutaneously or calcium gluconate 10 cc intravenously may be given

If ergotamine is contraindicated or must be discontinued other drugs that will produce arterial constriction may be tried Dihydroergotamine is less toxic than ergotamine and may be given in 2 to 4 mg doses intramuscularly (Horton) Ergobasine tartrate or ergotrate (0 2 mg intramuscularly) is not as effective as ergotamine Ephedrine benzedrine and pituitrin are either less effective or produce undesirable concomitant reactions Only caffeine as caffeine sodium benzoate 0 3 to 1 0 gm or as black coffee offers help without unpleasant side effects It may also be given in smaller doses combined with ergotamine (1 mg of ergotamine to 100 mg of caffeine 2 tablets at the onset of a migraine attack) as originally recommended by B T Horton Combined with analgesics and sedatives caffeine has been used against migraine for many years The benefit of octin (Palmer) appears to be doubtful

It should be understood that when given in amounts high enough to raise the systemic arterial pressure this first group of remedies will fail to show beneficial effect This must be kept in mind particularly when ephedrine or caffeine is used

Histamine for the treatment of migraine has been employed intravenously by Butler and Thomas and both intravenously and subcutaneously by Horton and Macy who prefer the latter method. The doses to be given will be described later in the section on Histamine Headache It seems rather characteristic that Horton and his co workers should find a greater percentage of significant improvement in patients with atypical migraine than in those with the typical variety "Although more than 75 per cent of all patients treated showed a significant improvement during the period of treatment practically every patient experienced a recurrence of migrainous attacks when histamine therapy was decreased below an individual critical level or was stopped entirely"

The beneficial use of histamine in migraine appears surprising in a condition where vascular hypotonicity and increased pulsation are already present and causing pain The explanation suggests itself that any amount of histamine or for that matter amyl nitrite acetylcholine and similar drugs large enough to cause a drop in blood pressure will diminish or even stop the transient migrainous headache which once the blood pressure has regained its initial level will be replaced by a headache of mixed origin due to relaxation of both intracranial and extracranial arteries The better results gained by constant subcutaneous subclinical doses of histamine are obviously much more of a preventive than a curative character

Analgesics and narcotics are the most frequently used drugs against migraine their common characteristic being to raise the threshold to pain In measuring the effect of these various drugs H G Wolff has found that 0 3 gm acetylsalicylic acid equals 0 3 gm acetophenetidin Both elevate the pain threshold 20 to 25 per cent for about 1½ hours larger amounts (1 to 2 gm) for from 2 to 24 hours Pyramidon (amino-pyrine) 0 3 gm with or without caffeine 0 15 gm given several times a day often alleviates the pain but presents the danger of possible agranulocytosis Antipyrine (phenazone) 0 3 gm is also frequently used although it is even more poisonous than acetanilid and phenacetin It seems reasonable therefore to give preference to the relatively harmless acetylsalicylic acid which particularly when taken with an alkali will cause hardly any undesirable reactions Where analgesics prove to be ineffective codeine phosphate 0 06 gm will often be helpful particularly in migrainous attacks with violent nausea and vomiting Here the subcutaneous route is preferable

The older especially the older French literature contains so many observations pertaining to the close relationship between migraine and gout that provided such a coincidence is established in a given case an appropriate treatment may be tried

The treatment of a status migrainosus may be difficult because of the unfavorable emo-

tional excitation apprehension and depres sion with which so many patients react to the extremely wretched and miserable condition that may last uninterruptedly for days As is generally known the drugs usually given for migraine even ergotamine used intraven ously have but a short and unsatisfactory effect on the patient s misery Codeine 0 1 gm subcutaneously is often necessary and may have to be administered repeatedly Morphine with its danger of addiction should be prescribed only exceptionally and not a few patients experience increased nausea and vomiting after taking it Demerol

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darkened room and given cracked ice by mouth in order to counteract the nausea and vomiting The stomach is better kept empty and fluids if necessary may be given intra

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ay dely the physician s greatest diligence and the best nursing care is often most suc cessfully treated by intravenous "anesthesia" Sodium amytal 0 5 gm and if necessary

larly will if absolutely necessary prolong the sleep sufficiently to help the patient over his attack The rare cases of status migrain osus with papilledema (indicative of brain swelling) demand intravenous infusion of hypertonic (sucrose or albumin) solutions

Occasionally a patient finds that once some treatment has cut short his premonitory symptoms the usual headache will be aborted For treatment of this pre headache phase of migraine many different vasodilating drugs have been used The good results of daily subcutaneous treatment with histamine in certain cases has been already mentioned However continuous histamine injection treatment of an illness which ordinarily has remissions of weeks and even months does not appear ideal The reader will find himself more confused than informed by the many claims of this or that substance offering the abortive treatment of a migraine attack. Both O_2 and CO have been acclaimed and it is true that they may occasionally help but it is equally true that their action is unpre dictable The well known vasodilators such as sodium nitrite and glyceryl trinitrate though effective in doses of 0 05 gm and 0 0005 gm respectively may help to abolish the symptoms of vasoconstriction but they may also precipitate the headache phase The simplicity of the procedure recommends the use of amyl nitrite in perles which in haled from a handkerchief may abort an at tack (but so may a glass of brandy or whisky) Nicotinic acid (niacin) may be taken in tablets as a vasodilator over long periods of time Atkinson prefers the com bined peroral and parenteral administration of 50 to 100 mg In cases with severe cerebral angiospastic phenomena (such as hemianop sia or hemilateral motor or sensory disturb ances) the intravenous injection of approxi mately 100 mg of the niacin or 30 mg of the amide is more reliable than when given by other means The number of drugs used for the same purpose is considerable The xanthines mecholyl doryl and many other antispasmodics have proved to be helpful in individual cases only to fail when tried on a larger group Papaverine should be given intravenously in a dose of about 0 1 to 0 2 gm Many physicians prefer the use of sedatives which like phenobarbital (0 05 gm three times daily) can be taken for long periods and can raise the threshold of visceral response The bromides also are used for the same purpose There is little doubt that reg ular sedation acts primarily on the general rate of emotional tension and nervousness an important factor in the precipitation of

cerebral arteries is uncertain and it is too dangerous a drug to be used for preventive purposes over a long period of time

In a disorder like migraine where our

nervous tension poor adjustment neurotic solutions of conflicts morbid attitudes anxiety etc plays an important role in the management of patients with migraine and it appears probable that not only sedatives

but any long utilized regimen and medication are often successful, less because of any specific effect than because of the reassurance and confidence derived by the patient from such a treatment The importance of psychotherapy in migraine cannot be overstressed As long as it does not demand great experience and special technic psychologic treatment can well be left to the general practitioner and internist The first rule is genuine and personal interest in the patient's problems Personal acquaintance with the patient's family, his environment, type of work, and hobbies places many a practitioner in a good position to understand the case The

tioner will find a clear and understandable analysis of the various personality problems and difficulties of these patients, and also good advice on how to treat them A neuropsychiatrist should be consulted where nervousness, sense of failure, fear, frustration insecurity, aggressiveness, etc, are conditioned less by existing or known circumstances than by the manifestation of a defective nervous, neurotic personality with long history of nervous symptoms

The importance of allergy in migraine has been considered for many years (Bassoe Best and Taylor, J W Scott), and parallels have been drawn to the mechanism of asthma and migraine To support such a concept, the effect of infections on migraine and the occasional eosinophilia of the blood have been pointed out Certain foods may precipitate attacks in predisposed persons Thus it appears reasonable that allergy studies should be made in migraine patients, particularly in the face of other evidence, e g, urticaria of an allergic condition Often chocolate is found to serve as an antigen in persons afflicted with headaches The evidence of histamine sensitivity in itself does not prove an allergic condition, although excessive amounts of histamine are produced in allergic reactions and may precipitate headaches by vasodilatation Antihistaminic treatment is discussed under Histamine ... treatment

is not rare and can be treated relatively easily by desensitization As a nonspecific treatment the intravenous injection of from 0 5 to 2 0 cc of a 5 per cent solution of peptone may be tried These injections are given twice weekly at first and then continued at lessened frequency until finally one injection per month is given Before a migraine attack gets under way, the use of calcium lactate or

ever it cannot be denied that many headaches, including migraine, are precipitated by an intestinal disturbance, especially by constipation, a condition which should be eliminated in every migraine patient

Endocrine disturbance or fluctuations at least as conditioning factors, appear often in the history of migraine The peculiar relationship of spells to menstruation pregnancy, and the menopause seems to support such a concept Yet, in reality, a change in the patient s activities and attitudes may be more important than the endocrine element Treatment of migraine with pituitary preparations, theelin amniotin estrogens and gonadotropic hormones must always depend on a sound indication i e, on the evidence of a definite hormonal disorder A thorough study of the patient's endocrine status may ... treatment, but

treating migraine related to the menstrual period and that suffered by individuals of the so-called Lorain Levy pituitary type He used placental estrogenic substance 2 teaspoonfuls a day, increased to 4 a day before menstruation He relieved migraine occurring during the menopause by the use of alpha estradiol benzoate Patients with hypothyroidism and with basal metabolic rates of −20 or more per cent were benefited by thyroid medication, while the hypopituitary types improved with pituitary extract S A Kinnier Wilson has followed the rule of administering thyroid extract in small doses (seldom exceeding 0 12 gm night and morning) with a view of maintaining sympathetic tonus, and has had "impressive results" Treatment of

women with migraine by means of hysterectomy oophorectomy, and radium sterilization does not guarantee a cure and is not to be advised (Alvarez)

Other methods of treating migraine have been directed, with various results, against disturbed liver function although there is no proof that such a disturbance plays a significant role in migraine Among other remedies, the use of decholin or sodium glycocholate has been advocated In order *to overcome hepatic malfunction,* Ivy and his co workers have used chondroitin sulfuric acid, a substance employed by the liver in detoxifying processes Capsules of 2 to 3 gm were given daily by mouth after meals for periods of many months, and, as long as this treatment continued relief from migraine was observed Drewyer has reported equally good results in 67 per cent of his cases Occasionally, we, too, have seen good results

In the surgical treatment of migraine, the injection of a small amount of a 1 to 2 per cent solution of procaine hydrochloride around the temporal or frontal arteries is a simple procedure and may bring prompt relief from an acute attack Ligation of the temporal artery or resection of a small piece may prolong the "cure" for many months, but this should be done only in cases which do not respond to medical (or possibly psychiatric) treatment Some patients, whose pain is not relieved by ligation of the temporal artery but continues in a rather unusual distribution (in the face, below the eye, in the jaws, neck, and shoulder), may be relieved by ligation of the middle meningeal artery (von Storch) This operation was combined by Adson with removal of the superior sympathetic ganglion, cervicothoracic sympathetic ganglionectomy, and trunk resection—an operation which appears almost as excessive as the subtemporal decompression proposed for inveterate cases Instead one may try, in desperate cases, an alcohol injection of the gasserian ganglion or a partial resection of the trigeminal roots, leading to an analgesia over the forehead, front and temple, and to freedom from headache The danger is the occurrence of trophic lesions of the anesthetized cornea Obviously, good results can be expected only when the spread of pain is limited to that portion of the head innervated by the fifth nerve Only rare and well selected cases should be chosen for this operation

The attending physician should be aware

usual types of trigeminal neuralgia, or from Sluder's neuralgia (attributed to infection of the sphenoid and posterior ethmoid sinuses affecting the sphenopalatine ganglion) These cases should be subjected to a treat*ment for migraine, especially to cold applica*tions and ergotamine injections, before the

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Wolff, would prove that the pain is due to dilatation, distention, and abnormal pulsations of the internal maxillary artery and its branches

Migrainous headaches in hypertension are discussed elsewhere

Painful muscular contractions about the head and particularly about the neck complicate many cases of migraine They may be due to the same vascular dilatation and distention as those observed in the temporal artery, but the fact that these neuralgic pains usually persist between the migraine attacks and as a rule do not react to ergotamine, as well as the sensitivity of the muscles to pressure, characterizes them as muscular pains As such they are nonspecific and occur in the presence of many kinds of extracranial and intracranial abnormalities, but may also occur as the expression of emotional tension They respond to psychotherapy and often to physiotherapeutic management (see below)

Headaches after Skull Trauma Headaches associated with or following injuries of the head are of various types, the appropriate treatment depending on the nature of the damage incurred In injuries of the skull, the local pain and tenderness is a pain and not a true headache, and its duration is usually short unless there is a localized injury to a nerve branch, severe scarring, adhesions, etc. In such cases the injection of a few cubic centimeters of 1 per cent procaine solution, or even the excision of the painful scar seems indicated

It is only too well known that many individuals with head injuries complain not only of local tenderness at the site of the injury,

but of aches and pains about the head The majority of headaches after trauma consist of pressure sensations, a feeling of weight and tightness, aching pain with cap like distribution, painful pressure sensations over the vertex, at the base of the skull, over the eyes, associated with local tenderness, and occasionally dependent on certain positions and movements of the head These aches can be accompanied by giddiness, unsteadiness and dizziness The question as to the nature of such headaches and therefore also as to their treatment, is often difficult to answer There is no conclusive relationship between either skull fracture or the neurologic findings and these headaches, although dizziness, which after all is but another subjective symptom, accompanies them rather frequently The presence of painful meningeal injury and subsequent scarring has to be thought of In severe post traumatic headaches a spinal puncture may give valuable information and even a pneumoencephalogram may be indicated if such headaches last longer than about 3 months Either procedure by itself, and not always for understandable reasons, may put an end to the patient s complaints

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ment, may cause severe intracranial headaches [illegible] study would [illegible] and could e [illegible] least indicate the right treatment for such a condition It is evident that acute accumulation of blood in the epidural and subdural as well as in the subarachnoid, spaces causes headache, and this chiefly through displacement and traction on pain sensitive intracranial structures This headache resembles a tumor headache and usually disappears with the removal of an epidural or subdural hematoma (or cyst) and the spontaneous resorption of blood in the subarachnoid space

Like other post traumatic nervous phenomena, lasting headaches have been regarded as proof of increase of vascular sensitivity following trauma" (Friedman and Brenner), and have been likened to histamine headaches Painful pial and cerebral arterial dilatation (similar to the histamine effect) combined with various dilatation and traction pains may be justly assumed in post traumatic headaches with abnormally low spinal fluid pressure In such cases, where the liquor production is probably diminished, a horizontal position, or perhaps merely a bending of the head, may give relief, but the headaches will be abolished promptly by hypotonic saline solution intravenously (200 cc of a 0 4 per cent solution), and even more promptly by the restoration of the *intracranial pressure to its normal* level by intrathecal injection of normal saline solution

In many instances lasting post traumatic headaches are muscular contraction pains about the cranium, of the same type that occurs in migraine, and may result reflexly from all kinds of noxious impulses They may indicate a sustained postural muscle contraction as an expression of emotional tension, fears, etc The presence of localized pressure pain, usually in the back of the head and neck, the temples and elsewhere, makes one think of traumatic myositis (see below), fibrositis, or periostitis, a diagnosis difficult to prove and probably much rarer than the painful reactive muscular contraction Treatment of a circumscribed, painful muscular contraction can be accomplished by injecting about 10 cc of a 1 per cent procaine hydrochloride solution in the muscle One must be careful not to put such an injection close to the atlas If successful these injections can be repeated at 2 or 3 day intervals Hot applications are useful in treating these painful muscle contractions, and one can make use of the radiating heat of infra red lamps or the moist heat of hot packs which most patients prefer The heat should be applied [illegible] morning and night, and [illegible] immediate [illegible] for muscle [illegible]

tional or organic induration in a muscle Mild friction, gentle kneading, and slight vibration not painful to the patient are employed The pressure should be gradually *increased* and a gentle stroking massage should terminate each treatment If this therapy is well performed the patient should be relieved from his aches after each daily massage Stretching of the muscles, as well

as "pricking with a needle," is also recommended, but will only rarely show a result superior to that of heat and massage. Acetyl salicylic acid and mild sedation, such as [illegible]

often benefit from sedation. The emotional factor contributing to this kind of headache is usually obvious in the general tense and nervous attitude of these patients, and can be demonstrated by the frequently excellent, though transient, effect of sodium amytal, 0.5 gm intravenously. Psychotherapy in one form or another will usually help the physiotherapeutic management.

The high incidence of long lasting headaches after skull injuries, which in themselves can hardly explain the type and duration of the pain, calls for a possible prevention of post-traumatic headaches. Brenner and his co workers have found that the incidence of headaches after industrial accidents is suggestively higher than that following recreational and domestic accidents. They also found a high incidence of psychoneurotic manifestations prior to the accident in patients whose post traumatic headaches lasted for more than 2 months after injury. There is also a high incidence of chronic post traumatic headaches in individuals who, either immediately after the accident or later, show pronounced emotional reactions and mood disturbances, such as hypochondriasis, anxiety, irritability, apprehension, and difficulties in concentration, as well as great fatigability. Unfavorable life situations, especially occupational difficulties and pending litigation, have a pronounced effect on post traumatic headaches. H. G. Wolff found that almost three quarters of these patients had anxiety conflicts and that about four-fifths were actually psychoneurotic before they suffered head injury. Conflicts concerning compensation play an important role in at least sustaining many post traumatic headaches. Wolff cites the excellent therapeutic effect of an "accelerated convalescence" observed by many during World War II. No doubt many post traumatic chronic headaches are "iatrogenic," i.e., induced by the overcareful and anxious attitude and orders of the attending physician. Many such headaches may be avoided by limiting bed rest following skull injury to the minimal necessary period, after ascertaining the absence of intracranial damage. This does not preclude medical supervision as long as organic complications, such as a subdural hemorrhage, are to be reckoned with. Only too often the patient's fears of brain injury with anticipatory disturbances to follow reflect merely the physician's overcarefulness. The patient should be put at ease and reassured that no untoward aftereffects of his injury are to be expected. Patients who complain of post traumatic headaches which, like painful muscular contractions or migraine like headaches, betray a state of emotional tension, will derive relief and general benefit when, with the help of their physician, they learn to understand the true nature of their condition. Neurotic maladjustment of longer duration will necessitate treatment by a psychiatrist. Of decisive importance is the prompt and definite settlement of compensation claims for injuries. Many a post traumatic headache disappears automatically when a final settlement is reached and the patient can direct his hopes and energy to constructive ideas about his life and work, and is freed from feelings of frustration, resentment and anxiety which may dominate him as long as he is fighting for what he feels are well founded claims.

Referred Pain in the Presence of Pathology of the Nose, Ear, Eyes, and Teeth. Painful conditions of this type may assume the character of a true headache, but more often they are described as an aching pain radiating to this or that part of the head, face, or neck. Their treatment depends primarily, of course, on a correct diagnosis and then coincides with treatment of the basic trouble.

Headaches and pain of nasal and para nasal sinus origin are usually due to the inflammation and engorgement of the turbinates, the ostia, the nasofrontal ducts, and the superior nasal structures. This pain is felt as a referred headache in specific parts of the head, usually in the front (between the eyes), or over the vertex, when the superior nasal structures are involved, and in the temples combined with pain in the jaws, teeth, and the zygoma region, when the middle or inferior nasal structures are the site of the swelling and irritation.

Treatment of this headache and pain is directed primarily against the swelling of the nasal mucous membrane. Solutions of cocaine (0.2 per cent), procaine (2.0 per cent), neosynephrine (1.0 per cent), or privine (0.1 per cent) are employed locally. The use of the benzedrine (amphetamine) inhaler benefits many patients, but appears to be not without danger in coronary disease. Ephedrine sulfate, preferably as a sterilized 1 per cent solution in 0.9 per cent saline, produces prompt shrinkage and can be used as a spray or nose drops. These drugs may be combined with local chemotherapy and with any kind of treatment directed against the nasal condition. The usefulness of hot packs and steam in headaches caused by inflammatory conditions in the nose and sinus cannot be overemphasized. Acetylsalicylic acid, 0.5 gm., given repeatedly, aids the good effect of heat. Only more serious underlying conditions such as periostitis, osteomyelitis, and epidural inflammation necessitate the use of codeine or morphine. Here also we mention the surgical treatment of organic nasal obstructions (septal deviations and polyposis), which, particularly in combination with vasomotor changes in the mucous membranes, can be the cause of headache.

Headache originating in the ear often occurs as referred pain in different parts of the head because the nerve supply is so diverse (the fifth, seventh, ninth, and tenth nerves, as well as the upper cervical roots for the scalp and muscles in the vicinity of the ear). For the most part, pain in the ear and pain referred from the ear occur in destructive or inflammatory ear disease and are often combined with painful contractions of the neck muscles leading to a tilting of the head to the diseased side. Periostitis and inflammation of the dura (extradural abscess) cause local pain and tenderness as well as more diffuse headache, over and behind the ear. Treatment corresponds to that mentioned in the foregoing section, and is, of course, primarily an otologic problem. However, it should be remembered that pains in the ear and headaches around the ear may occur also as referred pain in the presence of disease in other parts of the head and neck, e.g., the nasopharynx, larynx, teeth, temporomandibular joint, and upper cervical spine. Neuralgia of the fifth and ninth nerves, and particularly of the geniculate ganglion (Hunt's syndrome) includes ear pain as a more or less characteristic symptom.

Headache apparently originating in the eye is often treated as ophthalmic, not always on sufficient evidence and therefore often unsuccessfully. Wolff has concluded that pain from increase in intra-ocular pressure radiates to the entire distribution of the ophthalmic branch of the fifth nerve and may be accompanied by nausea. Only traction of the extra-ocular muscles and of the iris is painful. Artificially induced hyperopia and astigmatism (but not myopia) cause headache. Cushman found that refractive errors present for many years seldom cause headaches unless additional factors, such as overexertion, overuse of the eyes, psychic disturbances, and other illnesses enter into play. This observation is borne out by the fact that it is usually long-lasting eyestrain (caused by reading, etc., particularly in poor light) that, in persons suffering from hyperopia, astigmatism, or muscle imbalance, causes frontal or occipital headache. Many of these patients are aware of eyestrain and, in addition, complain of unpleasant sensations within the eyes and of eye fatigue. (Heterophoria or muscle imbalance can be assumed when the closing of one eye eliminates the headache.) Treatment consists in correction of whatever physical disturbance has been established.

The intense pain in glaucoma is usually worse in the early morning and is often accompanied by increasing headache with occasional nausea and vomiting. Pressure on the eyeball intensifies the headache, and

solution intravenously may be given additionally.

Intra-ocular inflammation causes ache around the eye and the temporal region, as well as intra-ocular pain and photophobia. A 1 per cent atropine solution in the conjunctival sac usually helps to relieve the headache and pain, but codeine and morphine injections may be necessary. The treatment of headaches which may be associated with inflammation of the cornea, conjunc-

tiva, or the optic nerve is part of the specific therapy of these conditions

Headaches associated with toothache and also those which sometimes follow dental extraction, are rather infrequent In acute cases the radiation of pain from the source of infection, i e, from the decayed tooth or from the tooth socket, is usually obvious and disappears with elimination of the source Electric stimulation of such a tooth will aggravate or precipitate pain and headache In doubtful cases, local anesthesia around a suspected tooth will abolish irradiating pain and ache if the condition of the tooth is the cause of the distress Treatment of such headaches should be directed primarily against the source of pain and headache

Occasionally one finds *disease of the temporomandibular joint* as the cause of headaches Costen has described this syndrome in which the headache is usually localized in the supra orbital and temporal region, but can spread to the vertex and occiput The displaced condyle of the mandible may also cause tinnitus and other unpleasant sensations in the ear as well as impairment of hearing Disturbance of saliva secretion is a frequent concomitant This malocclusion headache is often promptly relieved by interposing a flat object between the jaws and by correction of the overclosure

Occipital headaches and pains irradiating down into the neck and shoulders may accompany any of the painful conditions described in nose, ear, eyes, and teeth but are caused by muscle contraction Their functional nature and their treatment have been previously considered

Headaches from Cervical Myositis Myositis is supposed to be one of the most frequent causes of headache In a number of patients the diagnosis of infectious myositis is probably correct, although there is no histologic proof of such a condition Distress is usually felt as a deep ache or pain in the neck and occipital region sometimes localized in the skull itself Any movement of the neck, particularly after the head has been kept in the same position for some time, as after a night s rest, initiates or aggravates the pain Even slight manual pressure on the scalp of the occiput and on the neck muscles is painful The pain is steady and may be associated with nausea, dizziness, and sometimes anorexia It may irradiate to other parts of the head or down the neck toward the shoulders The palpating finger usually detects extremely painful, indurated nodules in the scalp and in the involved musculature This rheumatic headache (so named by Osler) is distinguished from muscular contraction headache (described above as the effect of emotional tension) only by the circumstances, e g, general or local infection, toxic conditions, effect of cold, drafts, etc, which characterize the clinical picture of myositis Not so rarely disease of the cervical spine, usually arthritic but sometimes traumatic, may be the cause of "rheumatic" suboccipital and neck pain and headache The correct diagnosis will indicate the appropriate treatment

The treatment of true myositic headaches corresponds to that outlined in the section on Post-traumatic Headaches In severe cases immobilization of the neck and support by a collar, as well as liberal use of acetylsalicylic acid is recommended The local infiltration of the painful muscle with 10 to 20 cc of 1 per cent solution of procaine hydrochloride may be tried in cases which do not respond to local heat, massage, and "antirheumatic" liniments The therapeutic procedures used in fibrositis in general should also be applied in rheumatic headache Cases which do not respond to such treatment within a few months, and cases where bone disease or a focal or general infectious condition as well as some other primary headache are ruled out, should always be suspected of being "tension" headaches and be subjected to a psychologic approach

Headaches in Temporal Arteritis. Temporal arteritis was only recently described by Horton, Magath, and Brown The painful-

sometimes also localized in the jaw and teeth, zygoma, ear, and occiput—all this in a patient, usually past 60, suffering from a fever and complaining of malaise, anorexia, and weight loss, distinguishes this condition from headaches due to other intracranial or extracranial sources Unlike periarteritis nodosa and disseminated lupus, with which temporal arteritis has certain histologic find-

ings in common, the temporal "arteritis" is usually restricted to the arteries of the head (H G Wolff therefore recommends the term "cranial arteritis") and is limited in duration Inflammation of the central retinal artery and of brain arteries may complicate the picture Treatment of these headaches and pain is purely symptomatic, although an attempt to control the underlying infection with antibiotics, etc, should be made

Headaches after Spinal Puncture. Headache *here results from the drainage* of large amounts of spinal fluid or from postpuncture leakage Not every patient complains of such headaches after lumbar puncture, and one may see sequelae more frequently in patients who show no evidence of brain pathology The headache is dull or throbbing *sometimes more suboccipital,* sometimes more frontotemporal

Treatment aims at a restoration of the ratio of brain volume to spinal fluid volume The volume of the spinal fluid may be restored to normal by replacing the amount of fluid withdrawn by physiologic saline solution, but such a procedure will not prevent further leakage Only the use of a fine puncture *needle will help prevent this undesirable* complication. The intravenous administration of hypotonic solutions, e g, 50 cc of 0 225 per cent saline, as recommended by Reese and Shulak, or a greater quantity of *a less hypotonic solution, may abolish the* headache Inhalation of amyl nitrite, which augments the brain volume by arterial dilatation, may be tried, but its success is rather unpredictable The best treatment still is to keep the patient in bed with his head lowered and possibly lying on his stomach during *the first 24 hours after puncture* Bed rest should be extended as long as the upright position causes recurrence of headache Oversensitive patients may develop postpuncture sequelae of a purely functional type, especially occipital headaches due to muscular contractions, particularly in the suboccipital *neck region (see above)* The administration of salicylates, mild sedatives, or 0 05 gm codeine, immediately after the puncture will help to prevent such reactions The suboccipital puncture of the cisterna magna avoids postpunctural headache, but this procedure, though not at all difficult, should be *reserved for* those physicians who have had considerable experience with the method True meningitic reactions, including severe headache after spinal puncture and originating in an aseptic meningitis, are rare, *and usually disappear spontaneously* without specific treatment

Histamine Headache and Headache in Infections and Toxic States. B T. Horton has called attention to a peculiar type of headache which he first called erythromelalgia of the head, then histamine cephalalgia, and which, *according to him,* resembles headache induced by injection of histamine This type of headache is of short duration, is not accompanied by premonitory symptoms, and may strike a patient several times within 24 hours Also, it may awaken him several times during the night It may disappear *after the victim arises, only to return* when he again falls asleep The headache is paroxysmal, chiefly frontotemporal, but occasionally occipital, and is accompanied by nasal congestion, flushing, increased perspiration of the affected side, and lacrimation Attacks come in cycles, to be followed *by long or short intervals completely free of* pain

*A true histamine headache is an intra*cranial arterial syndrome, while migraine is a predominantly extracranial one It would seem that the lack of response to ergotamine in the case of the true histamine headache *would be a simple means of distinguishing* Horton's cephalalgia, produced by a dilatation and distention of pial and cerebral arteries under the effect of histamine, from a typical or atypical migraine, caused by a painful distention of branches of *the ex*ternal carotid artery

Experimental and clinical evidence shows that the headaches so frequently complained of by patients with influenza, brucellosis typhoid fever, sepsis, malaria, typhus, etc., and those occurring after different vaccina*tions and injections of foreign proteins,* as well as after carbon monoxide poisoning and in states of cerebral anoxemia (e g, mountain sickness or sudden fall in blood pres*sure), are much like histamine cephalalgia* The same *holds true for headaches follow*ing the use of, or the exposure to, nitrites Cerebral vasodilatation and distention characterize all these headaches, just as they also explain the headaches in polycythemia vera,

the "postseizure headache" and the hypoglycemic or hunger headache

Treatment of this group of headaches should be directed against their respective etiologies, and thus necessitates first of all the diagnosis of the underlying infections

genic substances Horton has introduced the histamine treatment for histamine cephalalgia The lowered tolerance of individuals suffering from allergic reactions to histamine can obviously not be overcome by a desensitization to histamine since histamine is not an antigenic substance Yet there is good evidence that histamine given subcutaneously (Horton) or intravenously (Butler and Thomas) may restore the lowered histamine tolerance to normal The rationale of this treatment can be derived from the generally known fact that individuals suffering from headache under exposure to nitrites will often gradually develop a tolerance to nitrites and lose the headache

Here again it must be said that the success of the histamine treatment is not specific We have seen continuous histamine treatment effective in certain patients with different kinds of headaches (as in other vascular disorders) and it is well to remember that many years ago Gowers successfully treated migraine and migraine like headaches with frequent small doses of nitroglycerine

Horton and his co workers at the Mayo Clinic have been satisfied with the subcutaneous administration of histamine They found that 0 1 cc of a histamine diphosphate solution of 1 10 000 was satisfactory as the first dose and they recommend this to be given twice daily increasing it by 0 05 cc until a dose of 0 5 or 1 0 cc of the solution is reached They continue this last as a maintenance dose and give it one to three times a week F K Hansel found that smaller doses were even more effective and claims success with the sublingual application of 5 drops of a 1 2000 histamine solution or even of 2 drops of a 1 10 000 solution twice daily

The usual intravenous histamine treatment consists of the daily administration of 2 75 mg of histamine diphosphate in 500 cc of isotonic solution of sodium chloride Most patients tolerate the infusion of this amount of histamine and fluid given by continuous drip for about 1½ hours or even less The patient should not develop a headache or a histamine caused fall in blood pressure Such reactions can be controlled by reducing the rate of flow or by injecting 1 gm of ascorbic acid into the rubber tubing

Antihistaminic preparations including

patients complain of unpleasant side effects such as drowsiness sleepiness dizziness and nausea Whenever antihistaminic drugs are given the patient should be checked by his physician at least once a week a blood examination with a differential leukocyte count being made

The breathing of high concentrations of oxygen should be tried Wolff and Lennox have shown its constricting effect on pial vessels and Wolff has found it particularly successful in the treatment of headaches associated with carbon monoxide poisoning and other anoxemias the "postseizure headache" and the so called "hangover headache"

of ergotamine tartrate which is useless in cases of intracranial (pial or cerebral) arterial dilatation and distention Keeney recommends benzedrine and ephedrine but their efficacy would indicate that the condition under treatment probably belongs in the migraine group (see above)

FREDERICK HILLER

MULTIPLE OR DISSEMINATED SCLEROSIS

Although multiple sclerosis is one of the

logic maladies fill the doctor with a more humiliating sense of helplessness reflects

National Multiple Sclerosis Society may well

supply us with fuller knowledge and with better tools with which to combat this widely incapacitating disease

We know that acute lesions in the central nervous system are characterized by a general sparing of the axis cylinders in the demyelinating process For this reason many of the clinical manifestations of the acute stage and of acute relapses are reversible This explains the typical tendency of this malady to spontaneous remissions, which, when they occur following some treatment, only too easily give rise to therapeutic optimism and thus impede discernment of the sound rationale of an apparently successful therapy Since in chronic cases the pathology consists of foci of sclerosis, e g, of scar tissue, which of course cannot be influenced by any kind of treatment, whatever therapy may be tried will have to be directed primarily against the clinical manifestations in early cases and against acute aggravations and relapses in later cases

An objective and critical attitude toward the multiplicity of recommended therapeutic procedures is necessary if we wish neither to deceive ourselves nor to raise false hopes in our patients It can be safely assumed that every type of therapy used in multiple sclerosis is successful in about 45 per cent of the cases, this percentage of improvement in the patient s condition being approximately equal to that of the occurrence of spontaneous remissions Nevertheless, most of us make use of one treatment or another because we have the impression that remissions may be aided by our efforts, and that aggravations or relapses of the condition may be prevented Moreover, we feel that a hopeful or at least an active attitude on the part of the physician is essential to the patient s morale

A brief enumeration of treatments which have been or still are employed appears to be useful Going over Brickner's extensive tabulation, the reader is baffled by the similar ratio of success and failure of the most heterogenous types of therapy and he is finally convinced that none of the so called specific treatments achieves much more than does Nature in the form of spontaneous remissions

Anti infectious treatments, including those making use of almost all the heavy metals, have long been recommended The belief that multiple sclerosis may be caused by a spirochetal infection has encouraged treatment with neoarsphenamine and silver salvarsan, lately replaced by mapharsen The intravenous arsenic treatment, the injection of sodium cacodylate in gradually increasing doses, and the administration of Fowler's solution have so often shown a beneficial effect that many physicians, including experienced neurologists, feel that such an effect is not simply accidental Rather frequently one sees in multiple sclerosis a hypersensitivity to neoarsphenamine, shown particularly by high temperature for a number of days Although this complicating reaction, necessitating termination of the treatment, has been called undesirable and even contraindicative, especially good and prompt remissions have been observed after such febrile episodes

Serum therapy in different forms has been tried in vain A specific vaccine, such as Purves Stewart thought he had found has never existed Nonspecific vaccines have been used as polyvalent vaccines or as antityphoid paratyphoid vaccines in the manner usually employed in artificial fever treatment Pyrexial methods of this kind, or those involving diathermy (Neymann and Osborne), have been used by all of us with great enthusiasm at first, only to lead once more to doubt and rejection Malaria treatment was once supposed to help even chronic cases, but almost all cases of more than 5 years' duration did not respond well Bennett and Lewis met with similar results with the use of diathermy but found that early cases do seem to benefit from this treatment Most physicians, we think, agree with Freeman, who denies good results from fever therapy, even in acute cases Besides, fever, at least the kind produced by typhoid vaccines, shortens the coagulation time of the blood a condition which appears undesirable in view of the circulatory disturbances within the acute foci in the brain Finally all of us have seen acute exacerbations of multiple sclerosis during a febrile illness!

Roentgen treatment of the spine has been tried in a large number of cases, especially by French physicians, but without convincing results

Antimyelolytic effects have been attributed to the use of quinine (Brickner) Results of this treatment, too, were disappointing

Antithrombotic treatment has been introduced, dicoumarin being used as the anticoagulant Putnam and his associates have reported on this type of therapy which is neither founded on a generally accepted concept of the pathogenesis of the lesions nor supported by particularly good clinical results Most vasodilating drugs, such as nicotinic acid, nitrites, papaverine hydrochloride in tolerance doses, as well as aminophylline, have no effect on the clinical course of the disease That cervico thoracic sympathectomy should be of help, is, a priori most improbable, although a beneficial effect from this, too, has been claimed

Histamine, as advocated by Horton and used in many cases at the Mayo Clinic, has been tried by a goodly number of neurologists and internists The 1947 report of the National Multiple Sclerosis Society supports our impression that the daily administration of histamine by intravenous drip (2 75 mg of histamine diphosphate in 250 cc of isotonic sodium chloride solution) adjusted to the patient's tolerance and given on a full stomach, is generally well received Although at the beginning, a 1½ hour infusion period seemed optimal, we found that during the course of treatment, this period could be shortened to three quarters of an hour without causing headache and discomfort Our patients were subjected to from 20 to 30 infusions, but, contrary to the custom in other clinics, we always combined the treatment with complete bed rest Some of our patients received daily subcutaneous histamine injections (see the chapter on Headaches) for several months after their discharge from the hospital In the majority of acute cases or in relapses the active hyperemia of the brain brought about by the histamine and the complete bed rest, along with a high vitamin diet and general psychotherapeutic influence, proved successful To what extent the good results were attributable to the histamine remains an open question which can be answered only on the evidence of wide statistical material The idea that histamine may serve the purpose of desensitization has been abandoned (see also the section on the histamine treatment of headaches)

Antiallergic treatment with antihistaminic drugs has yet to prove its value

General Treatment Care of patients in the acute or subacute stage of multiple sclerosis deserves much more medical attention than it usually receives There can be no doubt that the acutely sick patient should stay in bed until all signs of activity of the disease process have disappeared This holds true not only for recent paresis and paralysis of the extremities, but also for cerebellar, cranial nerve lesions and for signs of retrobulbar neuritis The bed rest usually brings about both subjective and objective improvement and is recommended as long as such improvement continues Another indication for bed rest may be a pleocytosis of the spinal fluid, such an increase of cells revealing a meningeal reaction to the underlying lesion of the nervous substance Such patients should be kept in bed until the cell count has returned to normal A period of 1 to 2 months may prove necessary Although there is no proof of a specific effect of vitamins in this illness, they may be given and are certainly indicated in cases with evident vitamin deficiencies and in those complicated by anemia Concentrated liver extract, 1 cc intramuscularly twice weekly, combined with iron by mouth should be administered The results of monthly blood transfusions (300 to 500 cc each) have been praised by European neurologists who have seen surprisingly good reactions particularly in anemic and adynamic cases Results usually show up within a few days after transfusion and one often sees chronic complaints, such as headaches and paresthesias, disappear Constipation, a common complaint of these patients must be taken care of by proper diet, and, when necessary, by mild laxatives and enemas Urinary complications, often an early sign of spinal lesions, may occur in the form of frequency, retention, or incontinence Treatment corresponds to that followed in myelitis Great care should be given to urinary infections, which like all infections, tend to have an unfavorable influence on the course of the disease Urinary antiseptics, diuretics, forced fluids, and, if necessary, tidal drainage will have to be employed It goes without saying that the

patient should always be examined for any kind of infection and, once located, such foci must be eliminated

Once the acute phase of the disease has been overcome the patient, even though more or less handicapped, may be able to resume his normal activities, or, if afflicted with severe lasting disabilities, he may be in need of further treatment In the first instance the physician will be asked how to prevent further relapses, which in our experience threaten all patients with multiple sclerosis Among known precipitating factors, an important role is played by infections, overexertion and fatigue, chilling, emotional disturbances and pregnancy Although some women feel even better during pregnancy, onset or relapse of the disease is precipitated in about 40 per cent of female patients Serious consideration should be given to interruption of pregnancy with sterilization All patients should be warned against overwork, emotional strain, and exposure to cold and should be told how to protect themselves from infections, especially the common respiratory types which so often lower resistance and precede relapses Our experience supports Freeman's recommendation as to the value of a southern climate, where multiple sclerosis has been found more rarely than in the north Those patients fortunate enough to be able to exchange the cold, damp and rapidly changing weather of the northern states for the mild, dry, and stable weather of Arizona New Mexico, North Texas, and Southern California, should be encouraged to do so, even if only for the winter months

Symptomatic treatment can often bring improvement to chronic cases, so frequently incapacitated by spastic paresis, ataxia, and cerebellar disturbances As soon as the acute phase of the disease is terminated, trained physiotherapists should institute re education by occupational therapy and muscle training, gradually increasing active exercise with the help of warm baths, massage, and mild passive motion of the extremities It does not further rehabilitation to leave patients to themselves or to order them to remain inactive or even in bed One should do one's best to avoid the development of spastic contractures and deformities, and, once they have developed, relieve them by active therapy Drugs used in combination with physiotherapy include curare and prostigmine The best results with curare are obtained where spasticity is associated with good voluntary muscle power, but these results are fraught with the danger inherent to the drug D tubocurarine chloride in oil and wax may be absorbed rapidly or slowly in a rather uncontrollable manner, and dangerous respiratory difficulties may ensue Furthermore, ataxia may increase or become more incapacitating because of the vertigo following curare Its use should be restricted to hospitals, or at least to physicians with curare experience Strangely enough, prostigmine best known as a curare counteractant (see also the section on Myasthenia), benefits at least some cases of spasticity complicated by urinary difficulties, tremor, and weakness Kabat has used it in cases of from 1½ to 29 years duration with moderate to severe spastic paralysis mostly of a progressive type Success was attained, notably in cases with less severe paralysis, from daily intramuscular injections of neostigmine methylsulfate (1 to 3 mg with 0 3 mg atropine) usually combined with oral administration of 15 to 30 mg of prostigmine bromide, three times daily for a period of several months to 2 years

Myanesin (3 ortho toloxy-1, 2 propane diol), the latest of the antispastic drugs has been described by Berger and Schwartz as being ineffective in cases of contracture due to multiple sclerosis Further studies, however, may change this impression

Psychotherapy Psychotherapy in its widest sense is an important factor in the treatment of a disease which affects so many young individuals, strikes with such sudden paralysis or blindness, torments with such incalculability and capriciousness, and fosters such fear of incapacity and helplessness It is indeed surprising, but is possibly explained by the brain pathology, that not more of these patients show severe reactive depressive disturbances Relatively frequent are a lack of insight and euphoria which may alleviate mental distress but may also occasionally interfere with the plan of treatment In multiple sclerosis, hysteria is not only a frequent diagnostic error, but also a complicating factor Such patients, often bewildered by the coming and going of the

and cures by hypnosis, but more often it explains the good results of reassurance anxiety relief, inspiration with the will to live, and the will to overcome physical handicaps by readjustment The good physician never tells either patient or relatives that multiple sclerosis is a hopeless, steadily progressive disease In view of the fact that 5 to 10 per cent of the victims remain able to work with but few symptoms, that about 25 per cent are only moderately handicapped for a period of more than 10 years, and that many are incapacitated only for certain activities, who can make such a statement?

FREDERICK HILLER

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PARKINSONISM

Parkinsonism is a descriptive diagnosis synonymous with the manifestations of paralysis agitans certain postencephalitic states, and disturbances of the extrapyramidal system observed in cerebral arteriosclerosis (known as arteriosclerotic rigidity) and in various lesions of the brain The latter are also described as symptomatic parkinsonism and may be the result of severe intoxication e g, with carbon monoxide or manganese, but may also result from encephalitides other than epidemic encephalitis Of the degenerative diseases, hepatolenticular degeneration (Wilson's disease) produces a progressive extrapyramidal syndrome which may resemble postencephalitic parkinsonism

The treatment of parkinsonism is almost always purely symptomatic, and is directed against the three basic disturbances hypokinesis, manifesting itself in the reduction or loss of automatic movements, particularly associated synergic movements, and in the paralysis of spontaneity and initiative, muscular hypertonus or rigidity, and tremor

One, two, or all three signs of the disease may be present, varying in degree from case to case The three do not react equally well to the same treatment, thus necessitating therapeutic selection according to the preponderance of one or the other of the disturbances It should be remembered that the characteristic poverty of movement, the anomalies of posture and the loss of facial expression and of mimicry are by no means always the result of muscular rigidity, but may be independent disturbances Besides the tremor, other hyperkinesias include phasic, tonic, or tetanic muscular contractions, e g, oculogyric crises, sometimes tic-like involuntary movements, etc All are resistant to treatment

The treatment of parkinsonism is a lifetime affair for the patient This he must understand without discouragement Many of these individuals accept with relief the fact that their condition is not a true paralysis, and that, if they give their full co operation, appreciable improvement can be acquired and maintained Fortunately, many cases especially those of postencephalitic parkinsonism, become stationary after a number of years, and thus permit these patients, if properly treated, to continue useful lives and to get along much better than they would without any treatment at all We shall

tient should be told about the dryness of mouth and the difficulties of accommodation that he will experience but which are usually overcome with time Most patients compensate for the lack of saliva by chewing gum or by sucking fruit drops Others just accept the fact If necessary, pilocarpine nitrate, 5 mg or more, several times daily will alleviate the mouth dryness as well as the disorders of accommodation

In a great number of patients hyoscine (scopolamine hydrobromide) has proved to be not only an efficacious but a reliable drug over long periods of time Patients easily ad just themselves to the required dosage, habit formation appears to be almost negligible, and unpleasant side effects are controllable In cases of average severity the minimum dose is 0 5 mg three times daily, given by mouth in tablet form In milder cases or in apprehensive patients 0 25 mg can be tried, the dose being gradually increased to 1 5 to 2 mg daily A severe rigidity often demands much larger doses, and many of these patients finally take a regular daily dose of 10 mg without ill effects, although such a dose would have an extremely toxic effect on a normal individual Quite similar is the effect of atropine sulfate in the same dosage Resistant cases have been treated successfully for months with doses as high as 20 mg three times daily The danger of cardiac complications and of toxic psychotic reac tions must be kept in mind, and the patients should be closely watched Stramonium ap pears to be most useful in combination with scopolamine when this drug cannot be taken in sufficient amounts It may be given as tincture in doses of 25 drops up to 1 teaspoonful three times daily, or in powder form (in pills or capsules), 0 5 to 2 0 gm as the total daily dose Bulgarian belladonna, originally a white wine decoction of Bul garian belladonna root, can be obtained in tablet form as bellabulgara Fabing and Zeligs found the wine extract from the U S P belladonna root just as effective Patients who do not respond favorably to the other drugs named above may be given bellabul gara, which is supposed to be more effective in smaller doses A like claim is made for compounds of belladonna alkaloids, such as rabellon In every case the individual optimal dosage must be established

Since Price and Merritt's report on the treatment with wine extracts of Bulgarian belladonna, synthetic products with all the good effects of the belladonna group of drugs but with less toxic manifestations have been tried Berger and Schwartz have found that the oral administration of myanesin (about 1 gm daily) is useful in reducing not only the rigidity but also the tremor Hartmann has reported on a product called parpanit, which seems to have a good effect on the rigidity The reader will find more detailed information of this and of all these products, the value of which is yet to be proved, in the recent publications of Schwab and Leigh

Contraindications to treatment with the belladonna group include certain psychic disorders which may complicate posten cephalitic parkinsonism States of mental and emotional excitement and hallucinatory and paranoid conditions are aggravated by too large doses of belladonna and related drugs There is hardly any doubt that large doses of these alkaloids may of themselves produce toxic manifestations, such as dizziness, forgetfulness, confusion, lethargy, and hallucinations, and lead to inanition and prostration Organic debility of various types also may require caution in the dosage of these drugs

Curare, as d tubocurine, has no place in the treatment of the average type of parkin sonism, but it may be considered in those helpless and hopeless final stages of total rigidity where nursing care and nutrition have become almost unsurmountable prob lems

[illegible] f the [illegible]

fate) is added This is probably explained more b [illegible] effect of this drug, v [illegible] io- bilizes [illegible] fic effect on extrapyramidal mechanisms, although the stimulation of effective reactions (i e , subcortical functions) obviously plays an important role The dosage varies from case to case Usually 5 mg of benzedrine or dexedrine sulfate given in tablet form with the first two doses of scopolamine (at breakfast and lunch) are well supported and may be doubled if necessary Amphetamine

serves to be tried

The hyperkinesias, especially the tremor, are unfortunately rather refractory to all these therapeutic procedures Other drugs

a limited time (The reader is referred to the section on Epilepsy) Hemilateral severe tremor, which may reach such a degree as to become a torture to the patient, can be relieved by surgery Bucy has described the abolition of tremor by extirpation of a small portion of the cortical motor area (4γ) The freedom from tremor will have to be paid for by some motor weakness *

Almost every case of parkinsonism benefits from exercise, gymnastics, massage, and other physiotherapeutic procedures The physician who continuously and energetically insists on this part of the treatment will rarely be disappointed Any sports, such as bicycling, rowing bowling, swimming etc, may be employed to the same good end Many of the excellent results obtained with Bulgarian belladonna in Europe were due to the emphasis placed on gymnastics Physical exercise has proved helpful not only mechanically but also psychotherapeutically This has been part of the secret of success of those treatment centers for postencephalitic parkinsonism sponsored by the former Queen of Italy, where daily group exercises accompanied by stimulating music, formed part of the therapy We should remember that strong emotional reactions, precipitated not only by panicky fright but also by joyous elation can break through a severe hypokinesis and a considerable amount of hypertonicity The pleasurable character of the treatment and the ambition it arouses in the patient to win over his slowed down feeling can contribute decisively to therapeutic success

Frederick Hiller

* Doshay and Constable have recently advocated the use of trihexyphenidyl marketed under the trade name of artane, as a valuable drug in the treatment of parkinsonism This preparation may be used independently or in conjunction with other drugs such as ...

administer the drug before meals to diminish sialorrhea. The toxic effects of artane are minimal—*Editor*

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EPILEPSY AND THE CONVULSIVE STATE

The title of this section is selected because treatment in any instance must be directed toward orienting the patient and his family who are sensitive to the word "epilepsy" with its social implication We have come far from the dictum of John of Gaddesden, mentioned in Chaucer s Canterbury Tales, 1344, who said an epileptic "should not mingle with people to any extent, on account of the presence of his betters—before whom he is *ashamed* and by thinking of his condition, he falls ' 'Epilepsy" is derived from a Greek word meaning 'seizure" This seizure is caused by some disturbance in the body The convulsion or fit is only a symptom, just as "cough" in pneumonia, or "dyspnea" in heart disease The whole concept of stigma, social isolation, economic and educational handicap must immediately be corrected and the patient and family occupied with the problem of determining the origin of the epileptic state

This means a complete medical, neuro-

mental torpor, and are useful even when the newer drugs have failed

BARBITURATES These are essentially (1) phenobarbital (5, 5 phenylethylbarbituric acid) introduced for clinical trial in 1912 as a sedative and a hypnotic and tried in epilepsy by Hauptmann and (2) mebaral (3 methyl 5, 5 phenylethylbarbituric acid), *reported by Heyde and Blum in 1932 as a* useful antiepileptic drug

Phenobarbital is an effective substance against grand mal, jacksonian and convulsive attacks with localizing symptoms It is cheap but a bit more expensive when bought under trade names such as luminal and gardenal The principal limitation is its sedative effect but individual susceptibility varies Early, most patients feel drowsy but this disappears *The drug is excreted slowly so that it may* be taken only once or twice daily When well tolerated phenobarbital may be used for years without ill effect and without habitua tion Some patients, taking one 0 1 gm tablet at night, have been fit free for as long as 15 years

However, one danger exists If the drug has been used for years, abrupt withdrawal may be followed by an exacerbation of symp toms or even a status epilepticus When taken in huge amounts by mistake or with suicidal intent, the individual develops ataxia, coma, respiratory depression and may even die Picrotoxin and metrazol are antidotes, with oxygen and similar supportive measures A susceptible patient may develop a scarlatini-form rash

Phenobarbital is dispensed in tablets of 0 015, 0 03, and 0 10 gm , as an elixir contain ing 0 015 gm per teaspoonful or as a soluble sodium salt which can be used parenterally The drug may be combined with bromides hydantoins tridione, phenurone etc With *some combination as occasionally* in a pheno barbital mesantoin mixture excessive drowsi ness may occur

Mebaral or prominal, the N methyl de-rivative of phenobarbital is a barbiturate homologue of mesantoin The antiepileptic properties are less than those of pheno barbital Some *like to use it for petit mal* attacks, others like it as a supplement to tridione and also to reduce the possibility of a grand mal attack

The dosage is double that of phenobarbital, and the drug is dispensed in 0 03 and 0 2 gm tablets Somnolence, *as with phenobarbital*, may limit the total daily dosage which may vary from 0 10 to 0 6 gm

HYDANTOINS These are essentially two, sodium diphenylhydantoin (dilantin sodium) and mesantoin

DILANTIN SODIUM, epanutin, or phenytoin *sodium*, (5, 5 diphenylhydantoin) was recom mended for clinical trial in 1937 by Putnam and Merritt as the result of a formal labora tory experiment to find antiepileptic drugs Within a year the effective anticonvulsant effects were confirmed The use of dilantin sodium was recommended in psychomotor epilepsy in related behavior disorders and in symptomatic epilepsy Here for the first time was an antiepileptic drug which was not hyp notic. *Unpleasant side effects are several and* are often seen at the effective therapeutic level Two or 3 per cent develop a morbilli form rash A rare patient may develop a hemorrhagic reaction which on two occasions has been part of a fatal outcome from intake of the drug Muscle inco ordination with *ataxia of gait, tremor, nystagmus, diplopia*

plasia may occur, but this is usually amenable to dental care or to simple oral hygiene and vigorous massage Hirsutism appears rarely *in adults A few patients may suffer from* weight loss, drowsiness, fatigue, and even a psychotic episode

Generally the drug is administered in effec tive easily controlled dosages or combined with other drugs, phenobarbital bromides,

from 0 30 to 0 60 gm per day and children proportionately less

After prolonged intake of dilantin sodium a previously fit free patient may have a seiz ure Then combination with other drugs may *be necessary*

MESANTOIN, 3 methyl 5 5 phenylethylhy dantoin, was reported in 1945 and 1946 by Loscalzo, Clein Kozol, Lennox and Marburg and Helfand who showed that this drug could control many patients with grand mal or psychomotor epilepsy who were refractory to dilantin sodium or *other medication*

Others have stated that mesantoin is of no benefit to petit mal epilepsy

The toxicity is somewhat greater than that of dilantin sodium in that a substantial number of patients develop a generalized rash swollen lymph nodes in the scalp and neck and fever Drowsiness and fatigue may also limit the dosage Mesantoin has good anticonvulsant qualities and produces neither ataxia nor gingival hyperplasia As indicated above it may be combined with other drugs used in the treatment of epilepsy The tablet comes in one size 0 10 gm but a crease through the center enables easy division into 0 05 gm dosages The usual adult daily dose is 0 30 gm but as many as 9 tablets per day may be taken The combination with phenobarbital produces an effective antiepileptic substance but profound drowsiness may ensue

THE DIONES These are two tridione and paradione

Tridione or 3 3 5 trimethyloxazolidine 2 4 dione was synthesized and first reported to have analgesic properties by Spielman Everett and Richards in 1944 showed that tridione raised the threshold for chemically and electrically induced convulsions There is as yet no laboratory test for distinguishing drugs which would be effective against petit mal The specificity of tridione in the treatment of petit mal attacks was reported briefly by Perlstein in 1945 Lennox and others have confirmed these results and our experiences have been in consonance

Tridione is a remarkable drug against petit mal It may even have value in some psychomotor seizures when combined with dilantin sodium or phenobarbital It is generally conceded that tridione is somewhat of a convulsant per se and may increase the frequency of convulsions When grand mal

severe and occasionally dangerous side effects There is the usual rash of morbilliform character which clears with cessation of therapy and which may not be too severe if the drug is reinstituted slowly A strange side effect is photophobia on exposure to sunlight hemeralopia There is no known permanent damage to vision and the patient need only wear dark glasses The sensitivity wears off after the drug has been discontinued

A more serious complication is a depression of the bone marrow activity First a leukopenia occurs with a depression of the granulocytes Later the other blood elements become implicated so that an aplastic anemia ensues Several fatalities have been reported It becomes necessary therefore to follow all cases with frequent blood counts If the neutrophil count drops below 1600 per cubic millimeter the drug must be discontinued A relatively infrequent side effect is lethargy Nephrosis is also a rare complication

Tridione is dispensed in capsules contain

per day depending on the age of the patient and the need of the case

Paradione 3 5 dimethyl-5 ethyloxazolidine 2 4 dione was developed by Everett and Richards in the continuation of the research on oxazolidine diones It differs from tridione in the substitution of an ethyl for a methyl

patients who did not respond to the former

The over all effects of the two drugs are similar Paradione produces less photophobia is less toxic to the bone marrow and is less convulsant but it is also less effective in stopping petit mal attacks

Paradione is supplied in 0 3 gm capsules of which 2 to 5 may be required daily Blood counts and observations of mucous membranes are carried out as with tridione When grand mal attacks coexist dilantin sodium phenobarbital mebaral or mesantoin is appended to the regimen

PHENURONE Phenurone phenacetylurea *has recently been added to the antiepileptic* drugs through the studies of Gibbs Everett and Richards It has been reported as useful in grand mal petit mal and particularly in psychomotor seizures The greatest danger in use of this drug is with regard to the last group Phenurone tends to bring out and exacerbate previous personality deviations Therefore one must be on the lookout for released impulsive behavior psychosis and suicidal attempts All have been reported in

patients taking phenurone Individuals on this drug require the closest watching to rule out sensitivity

Other unpleasant side effects are anorexia which can be combated with large dosages of vitamin B complex tingling of the hands and feet palpitation and insomnia A rare rash and hepatitis have been reported and one of our patients invariably developed fever and leukopenia (no neutropenia) while on phenurone All of these disappear when the drug is discontinued

On the positive side however phenurone

with any of the other antiepileptic substances to produce more desirable over all effects

Adjuvant therapy in the treatment of epilepsy includes glutamic acid amphetamine and dexedrine caffeine ketogenic diet and dehydration

dullness I have never seen any of these salutary effects

AMPHETAMINE DEXEDRINE and CAFFEINE are of aid in combating the drowsiness of some of the antiepileptic substances and may be of use in the petit mal group where the spell is associated with a slow brain rhythm Caffeine is administered in dosages of 0 1 to 0 3 gm daily amphetamine up to 0 030 gm and dexedrine to 0 015 gm daily

KETOGENIC DIET is often beneficial in petit mal and myoclonic epilepsy However the

DEHYDRATION REGIMENS introduced by *Fay came along* with the studies on pitressin hydration tests for producing seizures The method is impractical over a long period necessary to control a given case of epilepsy

Status Epilepticus This is the great emergency of epilepsy and requires immediate treatment The repeated seizures must be

require repetition If such drugs are not available ether by mask may be tried Avertin per rectum is a useful drug and some advocate 10 cc of a 25 per cent solution of magnesium sulfate

Meanwhile the patient should be in a bed with padded side rails and adequate parenteral fluids (the patient is usually in coma or vomiting) with glucose and salt given to maintain fluid balance and keep the fever down Hypertonic glucose may be of value A maintenance dosage of sodium phenobarbital intramuscularly and sodium bromide by rectum is started Constant attendance is essential to prevent the patient from biting his tongue and injuring his limbs

As soon as the person can swallow the usual regimen of antiepileptic drugs is started but the parenteral route is used until the enteral intake is established

Furor States and Excitements These require special care because of danger to the patient and those about him While sedation and packs may control some many such episodes can be terminated only by giving the patient one or more artificial seizures Weinberg used metrazol but we have achieved excellent terminations of these states by use of electroshock treatment

Autonomic Diencephalic Fits These should respond to sympatheticommetic and parasympatheticommetic drugs but I have obtained one good remission in such a syndrome by progressive histamine desensitization

In conclusion therefore there is no single drug which suits any one type of patient Drugs dosages and combinations must be varied even in the same person who had been fit free previously for a long time until the desired remission is obtained Above all the

enough achieved but each year brings the answer closer to these many people who need help

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NARCOLEPSY

The treatment of narcolepsy depends a great deal on the diagnosis and while this particular book does not deal with diagnosis per se it is essential that certain points be emphasized

Narcolepsy or the tendency toward sleepiness is a symptom of many diseases which may vary from encephalitis brain tumor chronic uremia or heat exhaustion to altered metabolic states such as hypothyroidism or the complications of diabetes ketosis Many individuals under stress and strain become withdrawn and "sleepy" even the catatonic withdrawal of the more major psychiatric reactions is interpreted as sleepiness

In this section however narcolepsy will be limited to Gélineau s syndrome characterized by sudden attacks of

ing sleep and by associated bouts of cataplexy on emotional stimulation The individual loses muscle tone so that he may drop Acute excitement, laughter, anger, or surprise can leave the person absolutely help-

quently amenable to the action of the amphetamines Among these drugs may be mentioned amphetamine sulfate (proprietary benzedrine sulfate), racemic amphetamine *sulfate,* 1 *phenyl* 2 *amino* propane sulfate, d amphetamine sulfate, the other names (proprietary dexedrine sulfate) d 1 phenyl 2 amino propane sulfate, d benzedrine sulfate, methamphetamine hydrochloride, other names (proprietary desoxyn *norodin hydrochloride)* d *desoxy ephedrine hydrochloride,* the hydrochloride of the d isomer of n methyl betaphenyl-isopropylamine (1 phenyl 2 methylamino propane) Ephedrine sulfate, otherwise 1 phenyl 2 methylamine-propanol 1-sulfate, is also of use in narcolepsy

Amphetamine or benzedrine sulfate is a potent sympatheticommetic and central nervous system stimulant, counteracting sleepiness It comes in 10 mg tablets and is given in 20 to 40 mg dosage, once or several times during the day, as required Late dosages are avoided to prevent interference with regular sleep It is contraindicated in severe cardiovascular disease, marked hypertension, or hyperthyroidism Danger of habituation exists

produce the irritability, the peripheral vaso constriction and the elevation of blood pressure of ordinary amphetamine sulfate In narcolepsy it is given in 10 to 25 mg doses at intervals through the day

D desoxyephedrine hydrochloride, or desoxyn counteracts sleepiness without marked *peripheral pressor effects* It comes in 2 5 mg tablets

The action of the three amphetamines is essentially similar, the equivalents *being 10* mg amphetamine sulfate (benzedrine sulfate) 5 mg d amphetamine sulfate (dexedrine sulfate), and 2 5 mg of desoxyn Benzedrine sulfate is probably the most effective antinarcoleptic but it has the greatest number of side effects Among these may be mentioned anorexia, loss of weight jitteriness from the stimulating effect, and occasionally *elevated blood pressure* It may be necessary in some cases to increase the dosage of these drugs or to spread the administration over several dosages during the day

Another drug sometimes of value is ephedrine sulfate in dosages of ⅜ grain (25 *mg*) two or three times per day, as needed

It is again emphasized that the type of narcolepsy described here is that limited to the sleepiness with cataplexy The type asso

nomena due to third ventricle tumor, encephalitis, or metabolic disturbances are treated according to their causes Even in these disorders, the amphetamines and ephedrine sulfate may give symptomatic relief

BENJAMIN BOSHES

THE PARAPLEGIC STATE IN LESIONS OF THE SPINAL CORD

Physicians in general practice frequently encounter a paresis or paralysis of the legs, usually including also that of the bladder and rectum Occasionally, when the lesion reaches into the cervical spinal cord the upper extremities may be involved, as may *the cranial nerves and parts of the brain* when the disease is not limited to the spinal cord Treatment of a paraplegia is, of course, dependent first of all on a correct understanding of the cause of this paralysis In this respect each case will differ One may have to deal with an extramedullary lesion whereby a compression syndrome results from a *tumor, from an epidural abscess pressing* on the spinal cord, from a vertebral dislocation, or from the destruction of one or more verte [illegible] traumatic, [illegible] to an or [illegible] the continuity of the cord In other cases the lesion will be diagnosed as intramedullary, and *may be caused* by a myelitis, infectious or toxic in origin, by a tumor, by a traumatic lesion destructive, contusional or hemorrhagic, or by a *primary circulatory, i e,* ischemic, lesion Specific treatment will de-

Then and there will it be decided whether

the paraplegic state will be discussed here with the understanding that it may have to be preceded or accompanied by a specific treatment which will vary in every case

A few words only may be said as to the handling of acute traumatic paraplegics These patients should not be moved until the necessary means of transportation and sufficient help are available The head should not even be raised Three persons are required to slide the patient gently on the litter or to any firm surface used for transportation One man should use a steady traction on the head another on the feet and the third should take hold of the patient s clothing and thus pull him over on the litter The site of the spinal fracture or dislocation should be kept in slight hyperextension which is best achieved by putting a folded blanket under the shoulder blades or under the lumbar spine As a rule it is much safer to transport the patient in the supine position although certain spinal fractures may do as well, or occasionally somewhat better in the prone position Administration of morphine may be dangerous, particularly in high cervical cord lesions The acute root pain is often alleviated by the traction and by the body

chance to live through the usually many months of slow restitution or adaptation without suffering serious harm or even succumbing to the complications which threaten him in his paralyzed condition On the care and handling of these patients depends the final outcome of a paraplegia regardless of whether the anatomic continuity of the spinal cord is interrupted or whether only a more or less complete physiologic or functional interruption of the cord exists The attendin physician must often avail himself of th

therapy

Spinal surgery indications must be deter mined as early as possible This holds tru in all those paraplegias where a compressio syndrome has resulted from any conditio which strangulates the spinal cord An extra medullary abscess or tumor, a vertebral dis location or fracture, or a disease process i one or several vertebrae—all may cause wha is generally understood by the term, spina block A spinal puncture with performanc of Queckenstedt's test will determine th presence or absence of a complete block, but in a case of severe compression of the spina cord an incomplete block with a considerabl narrowing of the lumen of the subarachnoi space may still show an almost normal rise o spinal fluid pressure on jugular compression In nontraumatic cases a possible block shoul be verified as soon as possible, and the lami nectomy decision left to a neurosurgeon o surgeon In spinal injuries the decision t subject the patient to surgery is far mor complicated Such injuries with vertebra fractures or dislocations, demand, first o all immobilization of the patient Since lumbar puncture may be harmful to him, w therefore agree with John Martin's state ment "only those patients should have lum bar puncture manometric tests who ca be helped by operation" He considers "lam inectomy indicated in compression injurie of the cord only if there was an incomplet lesion and the patient was showing pro gressive loss of function, and the loss o function could not be arrested by close manipulation" Laminectomy in cervical in juries during the first few days, even in th presence of a block "is certain to be the on instance in which surgery contributes to th already poor prognosis of the patient" Since in many cases, the anatomic and physiologi interruption of the continuity of the spina cord cannot be differentiated, most surgeon agree that the presence of a block in th thoracic region, particularly with roentge ray evidence of severe bone injury, indicate laminectomy, even in the presence of a com plete functional loss below the lesion In

juries to the cauda equina offer far fewer *contraindications to surgery* and should be explored if there is roentgen ray or clinical evidence of root fiber compression or impingement by bone fragments

After the patient has overcome his primary shock spinal injuries with or without injury to the cord should possibly be corrected In injuries to the thoracic or lumbar spine the various methods of keeping the patient in hyperextension are indicated Injuries to the cervical spine are best treated with the application of head traction by means of the Crutchfield tongs The often severe root pains are usually relieved by traction and immobilization

Nursing care problems in relation to para*plegics center about lost or severely impaired* sensation and motion visceral and sympathetic disturbances below the level of the lesion and frequent motor phenomena originating in a spinal cord more or less completely severed from the controlling and integrating function of the brain Most of these cases are chronic and the morale of the patients depends greatly on the type of general treatment and on the psychologic attitude of the nurses and physicians

Decubitus ulcers have such a detrimental effect on the well being of these patients and *render their care so much more* difficult that they must be prevented at all costs Nothing leads so easily to the development of ulcers as constant pressure on anesthetic tissues particularly when associated with maceration of the epidermis by moisture such as sweat urine feculent material etc Plaster casts therefore should be avoided or at least most carefully applied and watched The turning of the patient at regular intervals (every 1 or 2 hours) *prevents damaging pressure* upon weight bearing points The Stryker frame permits turning the immobilized patient 180° allowing him to lie alternately on his back or on his abdomen Skin hygiene (washing massage alcohol rubs zinc powder or talcum etc) is as essential as the careful smoothing out of the bed sheet and the prevention of soiling by urine and eces The use of urinals or absorbent mate ' over the perineum the *regulation of* defecation the use of a firm mattress (if necessary a so called split mattress) have proved of *great* value The danger of excessive heat applications over anesthetic areas should be explained to the nurses The frequent profuse sweating can be mitigated by occasional injection of 0 4 mg of atropine *Once ulcers or bedsores have* developed dressings with sulfa powder or penicillin the use of ointments or the painting of the sore skin with tincture of benzoin *are preferable* to moisture incision drainage or débridement The healing process is facilitated by the use of sponge rubber air or water mattresses and by ultraviolet light Large and deep ulcers require surgery preceded and followed by penicillin therapy *The ulcer must be excised* in its totality and the underlying bony prominences should also be removed Tissue flaps turned or grafted *on such a clean and well vascularized wound* usually heal under a moderate pressure dressing

Nutrition should be sufficient (about 2500 to 3000 calories daily) and should be rich in protein and carbohydrates Vitamins in the form of multiple vitamin capsules are to be

Amigen or aminoids may be added to the diet Fluid intake should be generous The frequent achlorhydria in chronic paraplegics may be compensated by diluted HCl with meals Anemia which occasionally develops may benefit from liver and iron administration

Care of bladder and rectum is of greatest importance Not only is the urinary paralysis the most frequent and dangerous source of ascending infections (urinary sepsis has been the outstanding cause of insufficient and failing spinal reflex activity and finally of death and is still one of the gravest problems in chronic cases) but the lack of urinary and rectal control makes a paraplegic or paraparetic more of a cripple less fit to integrate himself again into human society

Any severe spinal cord lesion may show a bladder paralysis in the beginning In in*complete lesions only time can tell whether* the patient will regain his full or partially normal function of micturition or whether his bladder will retain one or another form of insufficiency Where the patient has lost voluntary control over his bladder treatment aims at the establishment of an "automatic

micturition Such treatment will also be helpful in furthering the restoration of partial voluntary bladder control should this state develop in time An automatic bladder may develop following lesions at any level of the spinal cord but develops more promptly in those above the middle of the thoracic cord Lower cord and especially cauda equina lesions are more often associated with a tendency to urinary retention increase of bladder capacity and incontinence Yet after many months of good care overcoming of infection and co operation of the patient an automatic bladder may be achieved even in lower cord injuries

A paralyzed bladder will first develop retention of urine followed by overflow and incontinence If not properly managed such a bladder may rupture and it is generally agreed that distention and overflow are harmful The arbitrary intermittent use of a catheter is bad since it facilitates urinary infection and sepsis and prevents the establishment of an automatic bladder Manual expression of the full bladder may lead to rupture and often aggravates an existing infection The best initial treatment of the paralyzed bladder is probably the so called tidal drainage a rather complicated procedure which can be carried out only in a hospital by those experienced in this method

For this reason these patients are usually treated by introducing into the bladder a number 18 Foley catheter which is small enough to permit the escape of urethral secretions into the bladder or externally An indwelling catheter such as this should be opened for drainage every 4 hours and should be closed with a stopcock Three times during the day and once at night irrigations with some urinary antiseptic are necessary Regular cystometric control gives information on the degree of muscular tone of the bladder and indicates when the catheter may be removed and the automatic emptying of the bladder be expected The efficiency of an automatic bladder depends on the patient s ability to achieve micturition at a desirable moment e g when the bladder contains about 300 to 500 cc of urine When the lesion is above the lower third of the thoracic cord this state of bladder distention is usually felt as sudden heat flushing and perspiration over the upper half of the body The patient then learns to initiate urination by the use of external stimuli e g rubbing the skin of the abdomen or that of the inguinal region tugging on one spermatic cord or pinching the skin of the thigh A good automatic bladder should empty itself when it contains 400 to 500 cc of urine and should retain less than 100 cc Such patients will empty the bladder about four times daily and may pass the night without voiding depending on the amount of fluid intake General muscular spasticity tends to diminish the bladder capacity and is often accompanied by frequent uncontrollable emptying of small amounts of urine

Lower thoracic lumbar and caudal lesions usually do not produce the viscero visceral reflexes and the initiation of an automatic emptying of the bladder often depends on a sensation of fullness in the abdomen Sometimes automatic micturition follows transurethral resection of the bladder neck This operation may be of value to patients with an automatic bladder impaired by retention due to spastic sphincteric contraction

The decalcification of the bones in recumbent paraplegics the excretion of large amounts of calcium through the kidneys together with some bladder infection often lead to stone formation in the bladder a condition which should be checked by bimonthly x rays A fluid intake of over 3000 cc combined with urinary antiseptics helps to reduce this complication Bladder stones will have to be removed Stone formation in the kidney pelvis and the passing of a stone through the ureter may betray themselves only by a rise in temperature

General experience has shown that patients with chronic cases of paraplegia kept alive with the help of modern antibiotic drugs can and must learn to empty the bladder automatically but it has also been observed that automatic micturition is easily lost if the patient does not get proper care or if he fails to co operate Relatively rare patients with completely flaccid sphincters may have to wear a urinal constantly

The often disturbing priapism which may be seen in compression or transverse syndromes alike responds to camphor mono- [illegible] in 0.2 to

Care of the paralyzed rectum aims at automatic defecation After a short period of complete depression of automatic function during the state of spinal shock the rectum will respond to stretching which causes contraction followed by relaxation Even though automatic defecation will develop in the presence of a spastic or flaccid sphincter, it has been found that lower spinal cord and caudal lesions are those most frequently followed by a satisfactory automatic defecation At first, the patient lying on his abdomen should receive enemas every 3 days only, and the formation of scybala may be avoided by the use of cathartics e g, mineral oil cascara, metamucil etc, for a few days in the transition period The sooner after a cord lesion reflex defecation is taught, the better First the attending nurses, then the patient himself, should stretch the rectal sphincter with the lubricated gloved finger Soon reflex rectal contraction and defecation will occur after slight stimulation of the skin near the anus, and eventually the patient will be able to defecate sitting on the toilet, compressing his diaphragm and using manual pressure on his abdomen

Treatment of pain becomes a necessity, not only in traumatic cord lesions but also in extramedullary tumors and in those cases where tumor metastases have invaded the spinal column Traction and immobilization often stop the root pain in vertebral dislocations and fractures Injuries impinging on [illegible] most frequently near [illegible] e sur [illegible] ay be [illegible] ig the posterior root fibers, can be relieved by posterior rhizotomy In the presence of lasting and severe pain below a cord lesion, not indicative of a root pain, cordotomy may be indicated, but not for pain in caudal lesions

Particular attention is to be given to the use (and eventually abuse) of narcotics That drug addiction is a dangerous complication in spinal cord lesions is testified to by the many patients so addicted who suffer pain or painful distress which defies treatment [illegible] sychotherapy should be given a chance in [illegible] cases

Treatment of muscle spasm in spinal cord lesions, both complete and incomplete, is a problem which has not been solved These spontaneous or induced flexor or extensor spasms are more frequent and distressing the higher the lesion Since spontaneous improvement may occur, radical operations, such as extensive anterior or posterior rhizotomy, should be reserved for chronic cases with complete physiologic transverse lesions of the cord Such patients who are in danger of developing unmanageable decubitus ulcers and show an increasingly hypertonic bladder, often become much easier to care for after section of the anterior roots, D_2 to S_1 In such cases a subarachnoid injection of 10 to 15 cc of absolute alcohol between L_1 and L_2 may be considered As a method, alcohol injection is of course, much simpler than the rhizotomy and quite as effective if done in the proper way, with the patient's legs and pelvis kept in maximal elevation for 24 hours after the injection This is also a highly satisfactory treatment for the frequent priapism The great drawback is its detrimental effect on a satisfactory automatic bladder For this reason alcohol injection should be limited to the treatment of severe spasm and mass reflexes in the completely paraplegic patient who, even after one year, has shown no functional return, and whose bladder is either atonic with excessive residual urine or hypertonic with a small capacity Whenever a spinal block, possibly due to a localized arachnoiditis complicates the condition, laminectomy or revision of the extramedullary tissue lesion is indicated Conservative treatment of muscle spasm involves the prevention of all irritating stimuli which initiate these reflex spasms, a task which in view of the very nature of the condition we must deal with is well nigh impossible Large doses of phenobarbital, 0 2 to 0 3 gm, deserve a trial The use of the galvanic alternating electric current, by which a tetanic muscle contraction from the anode is preferred may be given a chance, but it will usually fail to accomplish spasm relief *Peripheral nerve surgery* is employed with good results only for the adductor spasms, where section of the obturator nerves often leads to considerable improvement Once contractures resistant to conservative physiotherapy have developed, and hope for functional improvement has been abandoned orthopedic surgery may still contribute to getting a patient on his feet

The *rehabilitation program* of paraplegics

hospitals General practitioners in charge of individual cases will profit much by following the principles of this treatment and by securing not only the co operation of trained physiotherapists and nurses but also the active co-operation of the patients themselves (The reader is referred to the articles on rehabilitation by H A Rusk and by G G Deaver listed among the References for this section) Evaluation of the disability best done by a neurologist should precede the choice of treatment which should include *physical and occupational therapy* and the physical mental social psychologic and vocational adjustment of the patient to his handicapped condition Physical therapy started as early as possible should be directed toward improvement of voluntary muscle function and co ordination of movements toward prevention or correction of contractures and toward stimulation of circulation and of general body functions Aside from the special therapeutic measures already mentioned massage and both active and passive motions should be carried out several times daily and may possibly be combined with various heat applications under water exercises and systematic muscle re education Occupational therapy through carefully chosen activities has for its purpose the strengthening of weak muscles and the achievement of whatever use the patient can make of his paretic or paralyzed extremity Exercise and training of such muscles as were spared by the paralysis are particularly important In cases of injury or disease of the spine exercise must be postponed until the spine has become stable but after that the patient should be urged to move about in his bed to sit up to get on a chair etc Adaptive splints and other devices are necessary to help the patient use his extremities to stand up and finally to move about as much as he can A patient who is able to move his extremities under water and to swim will eventually be able to walk with the help of crutches and braces These mechanical appliances should be ordered and fitted by an orthopedist and where braces of the legs extend above the knee surgical shoes should also be worn by the patient

The final stage in the treatment of paraplegics is reached with the integration of the patient into some kind of useful existence Psychologic stimulation to this end is necessary and much responsibility rests on the physician and his helpers

Patients with complete transverse lesions of the spinal cord especially those with interruption of continuity at a high segmental level remain sensitive with regard to all vegetative functions L F Pollock and his co workers have demonstrated the lability of the blood pressure temperature regulation and urinary output all of which present functional deviations which deserve watching in these patients

Complications in paraplegics may be difficult to diagnose when they occur in anesthetic parts of the body and they may be of serious consequence in the case of intra abdominal disease Many paraplegics seem to be hypersensitive to the sulfonamides Osteomyelitis soft tissue abscesses and em

helpful in the prevention of embolism in the presence of thromboses of the deep veins Chronic rectal complaints associated with hemorrhages venous thrombosis formation of fistulas and fissures and prolapse of the rectum are frequent complications in cases of flaccid paralysis of the rectum and are often resistant to treatment

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NEURITIS AND BELL'S PALSY

Neuritis Treatment of neuritis is treatment of the great number of disturbances and diseases in which toxic, infectious, or degenerative lesions of the peripheral nerves play a more or less important role Frequently also included in the clinical syndrome, "neuritis," are the manifold traumatic nerve lesions and those cases of symptomatic neuralgia, which, accompanied by motor and sensory disturbances, e g, those affecting branches of the sciatic nerve, are the result of a compression or irritation of nerve roots In many instances the attending physician is able to find and to eliminate the damaging agent or condition, and, by so doing, will be applying the most successful treatment for the given type of neuritis This holds true, particularly, for the neuritis caused by external poisons and by deficiency and metabolic disorders, as well as for the traumatic (or mechanical) types of the disease In other cases, the general examination will reveal an acute or chronic infectious or toxic disease with the neuritis presenting only one of many manifestations Here the neuritis often outlasts other characteristic signs of the disease, as in diphtheria, for instance, and the physician would like to know what to do about it, and how to help the damaged nerves regain their functions This very same question arises, of course in another neuritic group, the one usually called "idiopathic polyneuritis," where exclusively nerve functions are damaged and where one obviously has to deal with an infectious or toxic agent, the affinity of which is limited or predominantly directed to the peripheral nerves or nerve roots, as in the Guillain Barre syndrome

General Treatment Management of the more acute phases of a toxic, infectious polyneuritis, with or without fever, consists of bed rest and warmth Heat is best applied locally in the form of hot packs or simply by the use of hot water bottles or electric pads under sufficient blankets If the legs only are involved, radiant heat from an electric arc is useful Heat usually has a soothing effect the pain, but should not be overdone, for an erythematous reaction of the skin is all that is necessary Many recommend the use of mud packs (*fango*), sand baths, diathermy, infra-red rays, etc All are useful in so far as they cause an arterial hyperemia without weakening the patient by too much perspiration Diaphoresis, using large amounts of hot fluids (lemonade, milk, or tea), sodium salicylate (1 to 2 gm), and a general wet pack, is an old, sanctioned treatment in cases where the general circulatory condition, especially, permits such a drastic procedure It is also customary to give potassium iodide (about 0 3 to 1 0 gm. three times daily, in enterically coated form) during the first week or two, and, if the patient shows no undesirable reaction, even to increase this dose until the nasal mucous membranes begin to show hypersecretion Sulfonamides, which of themselves occasionally produce neuritic reactions, are not recommended, but penicillin may be tried A total dose of about 10,000 000 units appears indicated in conditions which suggest an infectious etiology Aureomycin and chloromycetin, which may prove to be even more efficacious, still await trial Streptomycin's toxicity for the nervous tissues requires an absolute contraindication to its use

Local Treatment Local treatment of a painful neuritic condition employs hyperemia, not only by means of heat, but also by means of various rubefacient drugs, most of which are applied in the form of ointments Iontophoresis, whereby certain drugs are introduced into the body through the intact skin with the help of a galvanic current, has never become popular, and it appears doubtful whether, for instance, the use of a 2 per cent aqueous histamine solution applied from the anode, has a better vasodilating effect than the external application of a histamine containing ointment over a diseased nerve Other ointment ingredients which have a counterirritant effect, are methyl salicylate, eucalyptol, thymol, menthol, and methacholine Rubefacients, which had already proved their usefulness in our grandmothers' time, are liquor ammonii caustici usually applied as linimentum ammoniatum, and chloroform which, combined with *oleum terebinthinae*, is gently massaged into the skin After application of a counterirritant, wrapping the painful extremity in cotton often sustains the beneficial effect The use of electric current during the acute stage of a neuritis is not recommended,

not even the "anodal galvanization' Massage, if used at all, should be applied only in the most gentle fashion

should be given preference over aminopyrine and phenacetin, which when given too long and in too large doses, may have unpleasant toxic side effects Morphine, codeine and other narcotics should be withheld as long as possible, and then be given only under strict supervision and for a limited time

during the day or in greater doses for the night Most neuritic pains disturb the patient's sleep, and for this reason lower his threshold to pain

VITAMINS have attained an important place in the treatment of neuritis since the role of vitamin B_1 (thiamine) deficiency in the neuropathic manifestations in pellagra and its decisive curative effect on the peripheral neuritis in beriberi have become known We have gained the impression that an acute or an untreated case of polyneuritis, be it toxic infectious or of a clearly vitamin deficiency character, should receive thiamine chloride intramuscularly or intravenously in large doses After an intradermal test to rule out a possible individual hypersensitivity, 50 mg are given twice daily for about one week To use still larger doses may be indicated in desperate cases Ordinarily the patient will then be saturated with thiamine by the end of the first week, and should continue on oral thiamine, of which 10 to 20 mg daily will be ample The effect of thiamine is definitely enhanced by adding to it the other vitamins of the B complex This can be done properly by giving large amounts of brewers' yeast (50 to 60 gm per day) or the equivalent in the form of one of the many vitamin B or multivitamin preparations on the market Aside from thiamine (20 mg), such preparations should contain in one capsule niacin (50 to 100 mg), riboflavin (5 to 10 mg), pyridoxine (0 5 to 1 0 mg), and calcium pantothenate (1 to 5 mg), as well as vitamin C (50 to 100 mg)

Muscular Paralysis Treatment of muscular paralyses caused by peripheral neuritis demands particular attention The functional restitution of muscular power depends not only on the sufficient reinnervation of a muscle but also, especially in chronic cases, on the condition of the paralyzed muscles themselves It is generally understood that paralyzed muscles should not be kept in a state of prolonged tension and pull but it is equally important to prevent, if possible, a lasting complete relaxation of weakened muscles Muscular atrophy occurs rapidly, even in normal muscles, if the muscle is kept for any length of time in a state of complete inactivity, i e, if its points of fixation remain maximally approximated Therefore, the position of a paretic extremity must be carefully watched A footboard or a posterior leg splint will serve to prevent a foot drop, and a rolled blanket under the knees for a few hours daily will keep the quadriceps from remaining in a state of continuous relaxation Even more important is skilled muscle re education for the prevention of deformities and contractures Massage and both passive and active motion are applied according to the principles discussed in the section on Infantile Paralysis Electric current for the purpose of muscle contraction may be applied where no active motion is possible It stands to reason that faradization can be useful only in muscles which react to this current, which, in other words, do not show a degenerative reaction In the presence of interrupted innervation only galvanic stimulation with a current sufficient to produce a good muscle contraction makes sense Smaller muscles are more easily treated than large ones, in which a tolerable stimulus often produces only partial contractions To be successful galvanization should be done daily in a systematic fashion (for instance, 20 to 30 contractions a minute for 3 to 5 minutes twice daily) Galvanization helps to retard the wasting of denervated muscles and appears to be particularly indicated when reinnervation will probably take place Strychnine, usually administered as strychnine hydrochlorate, 5 to 20 drops by mouth (increasing day by day) is an old remedy in polyneuritis, but probably does not have more than a general tonic effect

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Bell s Palsy Treatment of Bell s palsy follows the same general principles as outlined above if the facial paralysis is of the so called "rheumatic or idiopathic" type One often has the impression that large doses of salicylates and an intensive diaphoresis in the earliest stage have a prompt effect on the paralysis In subacute or chronic cases slight massage of the face galvanization and once traces of active motion appear re education of the facial musculature by regular exercises before a mirror are necessary Statements made above concerning electrotherapy hold true for facial musculature also The very fact that about 75 per cent of cases of Bell s palsy recover spontaneously makes it imperative that the paralyzed facial muscles be protected from unnecessary wast

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One may assume that in a large number of cases a sudden increase of endolymphatic pressure precipitates the acute clinical attack The cause of this sudden hydropic pressure varies from case to case Mygind and Dederding attributed it to a disturbance of water and salt metabolism, but, as far as water metabolism, sodium retention, and serum potassium level are concerned, Talbott and Brown failed to show any significant deviations from normal in their cases Yet low sodium diet and dehydration are often helpful, and it remains undecided whether this is due to alteration in the normal sodium potassium relationship (Talbott and Brown) or whether this diet affects the electrolyte concentration and the hydration state of the tissues without producing a similar measurable effect in the blood

Treatment of Ménière's syndrome is still not successful in all cases, in spite of various often helpful therapeutic approaches Fortunately the vertigo not infrequently disappears spontaneously, or at least the vertigo-free intervals increase so that a marked improvement results The gradual diminution of hearing is usually but not always accompanied by a lessening of the vertigo attacks Loss of vestibular function in the affected ear may be followed by cessation of the attacks, but in a larger group of cases Walsh and Adson found that this is not the rule

Any kind of medical treatment of Ménière's syndrome depends on the occupation, intelligence, social status, and psychologic attitude of the patient These patients are usually extremely fearful and apprehensive, and need reassurance, which is often best achieved by explaining to them the true nature of their illness Promises as to the cure of their condition should be avoided, but they should be told that with their cooperation the dreaded attacks of vertigo may be overcome

Low sodium diet and dehydration (Mygind and Dederding) is one of the best means of treating these patients for any length of time Dehydration is carried out after the patient has been subjected to a water retention test With a normal fluid output, fluid intake should be restricted to 1000 cc or possibly less, whereas with a measurable water retention, fluid intake should be further reduced to accord with the extent that water is retained To start this treatment properly, the patient is best hospitalized, or at least kept under strict observation at home, for approximately 1 or 2 weeks Any therapeutic procedure which improves the general circu-

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kind of meals Salt substitutes may be used neocurtisal or cosalt being most useful In themselves they constitute the essentials of the treatment recommended by Furstenberg and by Talbott and Brown In our experience such large doses of ammonium chloride as Furstenberg recommends i e 9 gm daily for 3 days followed by a salt free diet for 2 days and continued in this way eventually and all too frequently cause unpleasant reactions such as nausea vomiting itching constipation and general weakness But smaller amounts are well taken for long periods The intake of this salt may be increased during relapses of vertigo The same thing is to be said concerning potassium chloride which Talbott and Brown have recommended in daily doses of 6 to 10 gm in aqueous solution It is true that potassium chloride is better tolerated than is potassium nitrate (Walsh and Adson) which most patients refuse to take for long periods but whether it has any specific action or merely acts first of all and possibly only as a diuretic is debatable The more chronic the cases of Ménière s syndrome the more must one adapt the treatment to what is compatible with a comparatively normal life These requirements are fulfilled by a low salt diet combined with a low fluid intake at a tolerable minimum and particularly in recurrent episodes of vertigo by the addition of about 5 gm daily of potassium chloride which the patient may use in crystal form in a salt shaker

Mercurials as diuretics may be tried in a particularly severe case but should not be repeated beyond the acute stage Regular bowel movements are necessary and non sodium laxatives are often indicated in order to accelerate dehydration The patient s basal metabolic rate should be determined and thyroid given as needed This may be a decisive factor in the process of tissue dehydration It goes without saying that sodium bicarbonate sodium bromide or any waters containing sodium are strictly forbidden

In patients with obvious vasomotor instability particularly in the presence of vasospastic phenomena elsewhere in the body (see above) and also in patients who do not react promptly to dehydration the [illegible] of histamine as employed by Sheldon and Horton should be tried Histamine acid phosphate 1 0 mg in 250 cc normal saline (or 0 8 per cent potassium chloride solution) given over a period of 1 to 1½ hours occasionally controls the acute symptoms of an attack It may be repeated once or twice the following days and if necessary can be given even for weeks Subcutaneous or intramuscular maintenance injections are preferable For the continuous treatment of these vasomotor disturbances the use of papaverine hydrochloride in tablets or capsules 0 1 gm combined with nicotinic acid in tablets of 50 mg three times daily is often beneficial This treatment should be kept up for months and reduced only gradually Nicotinic acid 25 mg intramuscularly as advised by Atkinson usually gives no better results

The tinnitus and the deafness improve occasionally under any treatment that affects the vertigo especially when the treatment is begun early enough However the majority of patients continue to suffer from their ear noises finding relief only by personal adjustment to this disagreeable symptom Even more patients fail to show any improvement in their deafness or in their distorted hearing, a feature that tends to grow worse with time Patients with evidence of a bilateral labyrinthine disturbance usually react less well to any kind of medical treatment

Many patients are so emotionally disturbed during acute attacks of vertigo or in anticipating relapses of their misery that sedation best combined with small doses of hyoscine may be necessary Others will have to be advised to restrict their activities at least for some time or even to make a change of occupation if sudden vertigo should mean great danger to themselves or to others Unless the disease has been controlled for many months patients suffering from Ménière s syndrome should not be permitted to drive a car

Surgery as treatment for the syndrome should be reserved for those rare patients who do not respond to any kind of medical treatment Frazier and Dandy have shown that intracranial severance of the eighth nerve is followed by "cure of the disease" Yet there are not a few instances where symptoms so abolished later appeared on the other side Portman s operation i e drain

age of the labyrinth through the saccus endolymphaticus in the posterior cranial fossa though acclaimed by some is criticized by others Destruction of the labyrinth or of a small portion of the semicircular canals appears to be a simpler and quite satisfactory method although tinnitus may sometimes persist The method used will have to be left to the surgeon—subtemporal destruction (Putnam) injection of alcohol into the external semicircular canal (Mollison) coagulation of the whole or a part of the end-organ (Day), or the much less harmful and rather conservative procedure recommended by Cawthorne and Hallpike who remove a piece of the membranous external semicircular canal or simply tear it across and who observe that this will lead to abolition of the vertigo but not of the hearing which together with the tinnitus may even show some improvement Provided the other ear is normal loss of hearing through an operation is not regarded as a contraindication to surgery since the hearing in chronic cases of Ménière's disease is usually so badly and disturbingly affected that nothing is gained by saving it

Surgical destruction of the labyrinth is usually followed by an acute exacerbation of the vertigo just as we see it in labyrin[...]ine injuries Rehabilitation after loss of one labyrinth is a necessary procedure and should start with preparing and training the patient for the unpleasant consequences of the operation The patient should be told that the vertigo will disappear in time and that physical exertion will be followed by easy fatigability which may last for months After the operation physical exercises combined with constant encouragement should be started as soon as possible The patient begins with head movements first with the eyes [...]d then with the eyes focused on near [...]hen on distant objects Special attention [...] to be given to the retraining of the [...]ion of position in space of the head as [...]s of the body and the extremities The [...]es are speeded up gradually and [...]and slow alternating movements must [...] ticed daily Within 2 weeks the pa[...] [...]ll be able to walk and with further [...]ties (turning stooping bending [...] up and down stairs etc) he will be [...]do light work by the end of a month

For a description of an elaborate and syst[...]atic rehabilitation procedure the reader m[...] consult Cooksey

Surgical removal of foci of infection aft[...] failure of conservative treatment should b[...] dealt with in every case of Ménière's syn[...]drome even though others have not achieve[...] Wright's excellent results with this as th[...] exclusive treatment

Frederick Hiller

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DISEASES OF THE SKIN

IMPETIGO CONTAGIOSA

This is a superficial type of pyoderma and may be produced by staphylococci or streptococci, more commonly by the former It is *highly contagious in the newborn*, fairly contagious in young children, and only mildly so in adults Infection is carried by the child's fingers, picking his nose or his cheeks

The disease is characterized by heavy, "stuck on" crusts, and the first indication of treatment is the removal of these bulky crusts This can be accomplished by thoroughly bathing them with a saturated solution of boric acid, then removing the crusts with sterile forceps, leaving a raw, oozing surface, which is then treated with an antiseptic ointment

One of the best ointments is ammoniated mercury incorporated in a greaseless base For children it is used in 3 per cent and for adults in 5 per cent strength Unfortunately some children are allergic to mercury, and for those individuals a 2 to 3 per cent vioform (Ciba) ointment may be used, or a 5 per cent penicillin ointment Occasionally penicillin will irritate the skin if it is used longer than five days If this, or any other of these ointments is too irritating the affected areas may be painted with a 2 per cent solution of gentian violet This stains the skin a deep [illegible] three [illegible] y

[illegible] eradicate the disease This treatment is not advisable for adults unless they are prepared to remain in seclusion

Ointments should be rubbed into the affected areas several times during the day and always before retiring The face should be washed twice a day at least, and men should shave every day While shaving may irritate the raw areas, it keeps the skin cleaner and hastens recovery

Inasmuch as the disease spreads by autoinoculation, it is well to have the patient wear white cotton gloves at night This lessens the danger of reinfection by scratching

In years past the tendency has been to use ammoniated mercury in 10 per cent strength This is too strong and may produce considerable dermatitis, 3 per cent is strong enough for children, and 5 per cent for adults I have also found pragmasul ointment of value

The disease may leave pink or red stains for a few days but no scars

EDWARD A OLIVER

ACNE

Acne is a disease of adolescence Comedo formation and increased oiliness of the skin appear about the age of 12 The disease may begin at this age and last until the patient is 20

The treatment is both general and topical General measures consist of the correction of constipation if it is present, either by care [illegible] the admis- [illegible]

[illegible] of water While the diet is not actually responsible for acne, it does play an important role in its etiology, and for that reason the patient should avoid chocolate, cocoa, gravies, greasy foods, nuts, and too much milk and cream Fatty foods, pastries, and creams also aggravate the disease Uniodized salt should be recommended to these patients to take the place of the commonly used iodized variety

The teeth should be examined carefully for abscesses, and the throat for signs of infection. If diseased teeth or tonsils are found, they should be removed

Regular bathing is important, but hot baths should be avoided Cold showers in the morning, followed by a vigorous rub

down, are beneficial, and do much to improve the general circulation

If the patient is anemic and underweight, suitable tonics containing liver and iron should be given

made in endocrinology, particularly in the preparation of anterior pituitary and male and female sex hormones, the hormonal treatment has as yet proved of little value

Vaccine treatment has not proved of much value, and most dermatologists have discontinued its use

Local Treatment The face should be washed thoroughly several times a day with a good toilet soap In the case of extremely oily skins, tincture of green soap may be used Cold cream must not be used Comedones should be expressed with a comedo expressor several times a week After bathing at night a sulfur lotion or ointment should be thoroughly applied to the skin and left on over night I prefer lotions, and two of the most popular lotions I use are

(1)	Sulfur precip	8
	Pulv camphor	4
	Acid salicylic	0 66
	Tragacanth	0 66
	Aqua dest ad	120
(2) Lotio Alba		
	Zinc sulfate	4
	Potassium sulfurette	4
	Glycerin	6
	Aqua dest ad	120

Lotions containing sulfur and resorcin are effective, though some patients may be allergic to resorcin One of the best of these lotions which seldom if ever, produces much irritation, is sulforcin lotion (Texas Pharmacol Co)

In obstinate cases with much pustulation and induration wet compresses of dilute Vleminckx's solution are effective Vleminckx's solution is made up of calcis vivae—15 sulfur sublimata—30, aqua—300 cc This is boiled down to 180 cc then filtered One tablespoonful is diluted to a pint of warm water and warm wet compresses are applied for 30 minutes to an hour every night

In every case of acne the scalp should receive careful attention Most cases of acne are accompanied by an oily, scaling seborrhea of the scalp, and this of course should be treated, as well as the acne For this the following ointment should be thoroughly rubbed into the scalp three times a week

Sulfur precip	3
Acid salicylic	0 33
Greaseless base ad	30

Another excellent lotion that also may be used instead of an ointment is

Euresol pro capillis	6
Hydrarg bichloride	0 18
Spts formicari	30
Spts *odorata*	30
Spts vini rectif	70
Aqua dest ad	240

This should be carefully applied to the scalp three times a week using the tips of the fingers or a small cotton swab

Roentgen therapy is one of the most effective methods of treating acne, and for boys and girls 17 years of age and over, it is the treatment that offers the most speedy and permanent cure I do not believe in its use for patients 16 years of age and younger The treatment should be given only by a competent dermatologist well trained in roentgenotherapy From eight to ten treatments of unfiltered therapy in doses of 75 r given once weekly to the affected areas, will effect marked improvement, and a perma-

duces the scars

Ultraviolet lamp therapy is often effective in milder cases, and may be used after the

and in that way lessening the amount of scarring that may appear in some cases

Acne Rosacea This affection is seen in older individuals In contrast to acne vulgaris which affects the face, the chest back, and shoulders, acne rosacea affects the face only, chiefly the nose, but also the forehead, cheeks, and chin The treatment of acne rosacea is both local and general The local treatment recommended is the use of lotio alba, just mentioned under acne's treatment,

and wet compresses of Vleminckx's solution In stubborn cases a 40 per cent sulfur paste is of great value The formula commonly used is

Sulfur precip	12
Ung petrolatum ad	30

This is not irritating, and is well tolerated by most patients

General measures to be followed are the careful regulation of the diet Anything which causes flushing or heating of the face, such as overindulgence in coffee tea, or alcohol, is to be avoided Chocolate, highly seasoned foods spicy foods, and fried foods are also taboo Acne rosacea is seen commonly in women past the menopause, so [illegible] should be [illegible] ed if present, and foci of infection in the teeth or tonsils should be removed

For internal use I place a great deal of reliance on ketochol a bile acid salt This is given in tablets—one tablet three times daily, after meals In my experience with the use of lotio alba and ketochol I have had excellent results

Vitamin B complex is highly recommended by many dermatologists, and dilute HCl in average doses also has been effective

When and if the condition has progressed to the stage of rhinophyma, surgical measures are indicated Surgeons remove these redundant masses of tissue with excellent results, by paring them down with a sharp scalpel No skin grafting is necessary

EDWARD A OLIVER

MYCOSES OF THE HAIRLESS SKIN

Tinea Glabrosa (Ringworm of the Smooth Skin) Superficial fungous infections of the skin may occur as scaling lesions, circinate patches solid plaques, or in gyrate configurations Some cases may stimulate the eruptions of pityriasis rosea, seborrheic dermatitis or eczema, and for that reason treatment should not be begun until the [illegible] may be found causing ringworm of the smooth skin the commonest of which is *M lanosum* The source of infection in this case is generally a stray kitten or some household pet which harbors the disease Finding the source is then easy

The most commonly used treatment is an ointment of ammoniated *mercury of 5 per* cent strength Anointing the affected areas with this twice daily for a week or 10 days, will cause the lesions to disappear rapidly Another ointment of value is one containing 3 per cent precipitated sulfur and 3 per cent salicylic acid and still another, useful for the dry, scaling types, is

Acid salicylic	1
Acid benzoic	2
Ung aq rosae	15
Ung petrolatum	15

Patches that are moist and eczematous should be treated with soothing lotions such as calamine lotion, or with wet compresses of aluminum subacetate solution, diluted 1 oz to 1 pint of cool water, before receiving energetic treatment, and a valuable ointment *if eczematization is present, is one* containing equal parts of daxalan ointment (crude coal tar ointment) and zinc oxide ointment The disease responds to treatment [illegible]

Tinea Crutis This rather common dermatophytosis affects the inner and upper part of the thighs, and is commonly known as "gym itch," "dhobie itch," or eczema marginatum It is caused by the *Epidermophyton inguinale,* and is generally contracted from *wearing infected articles of clothing such as* shorts, suspensories or jock straps

The localization of the infection is the result of the predilection of the fungus for intertriginous areas The same infection may occur in the axillae and about the anus

If the skin is dry and scaling, as it generally is in epidermophyton infections an ointment of 3 per cent precipitated sulfur and 3 per cent salicylic acid, rubbed into the affected areas once daily for a week or 10 days will readily effect a cure Resorcinol, 10 per cent in a zinc oxide and lime water *lotion will also cure it readily*

If, however, there is considerable inflammation present it is best to apply a 2 per cent aqueous solution of gentian violet until

it has cleared up This is applied once daily with a cotton swab, for 3 or 4 days, and when the inflammation has subsided the sulfur and salicylic acid ointment may be used until all signs of the disease have disappeared

Tinea Pedis (Ringworm of the Feet; "Athlete's Foot") This form of ringworm is so common that it has been estimated that from 50 to 90 per cent of the American public are afflicted with it sometime in their life

There are two different forms of this disease, and each is quite different from the other in appearance behavior and response to treatment

TYPE 1 This is a moist inflammatory type, due to infection with *Trichophyton gypseum* It is characterized by the development of vesicles and bullae on the soles and sides of the feet, by vesicular development on the toes and by maceration of the skin between the toes Subsequent rupture of these vesicles and bullae sometimes leads to secondary infection

Accompanying this type of infection, there is often an eruption of vesicles on the sides of the fingers and in the palms of the hands These lesions are known as dermatophytids or "ids" and are the result of the dissemination of the products of fungi on the feet through the blood stream

Inasmuch as this type is generally inflammatory when first seen the application of wet compresses or soaking the feet in antiseptic solutions is the treatment indicated Before using these solutions the distended vesicles and bullae should be opened and the debris cut away

The solutions most commonly used are aluminum subacetate solution diluted 1 oz to 1 pint of cool water, or a saturated solution of boric acid crystals in warm water and, if secondary infection is present, a solution of 0 25 to 0 5 per cent silver nitrate is of value

In using compresses, the patient should be instructed to keep them wet, and applied constantly for the first day or two After that he should use them two or three times a day for 20 to 30 minutes at a time

For a foot bath nothing is better than a warm 1 3000 solution of potassium permanganate, in which the patient soaks his feet twice daily for 30 minutes

As the inflammatory symptoms disappear, ointments may be used Desenex ointment, an undecylenic acid preparation, should be rubbed into the soles and between the toes, every night Another valuable ointment is Whitfield's ointment in half strength, the formula for which is

Acid salicylic	1
Acid benzoic	2
Cold cream	15
Vaseline	15

This too should be thoroughly rubbed into the affected parts every night

If there is no eruption on the soles and the infection consists only of maceration and vesiculation between the toes, painting these areas with a 2 per cent aqueous solution of gentian violet, a 1 per cent solution of iodine crystals in benzol or a 1 per cent solution of brilliant green will be beneficial

In these acute cases roentgen therapy hastens recovery, 75 r of unfiltered radiation to the soles of the feet at weekly intervals for two to three treatments produces rapid involution of vesicles and bullae and shortens the course of the disease

TYPE 2 This is a more chronic type, caused by *Trichophyton purpureum* There is practically never any vesiculation or inflammatory reaction in this type The plantar aspect of the feet is invariably involved, and the skin is dull red or brown in color, thickened, and the seat of a branny desquamation Where the hands are involved the palms, dorsal surfaces fingers, and fingernails are infected

In this type of the disease, ointments are the treatment of choice Full strength Whitfield's ointment of

Acid salicylic	2
Acid benzoic	4
Lanolin	15
Vaseline	15

is a valuable one and another that produces satisfactory results is anthralin ointment Treatment should be commenced with a strength of 0 1 per cent, and if this produces no irritation it may be increased to 0 25 per cent

It is the general belief that chronic cases are seldom cured, and that relapses after an apparent cure are more common than reinfections

Certain hygienic rules should be applied to every patient with ringworm of the feet. The shoes, slippers, and other footwear should be sponged out each week with a 10 per cent solution of formaldehyde, and should not be worn again for 24 hours, in order that contact dermatitis from formaldehyde may be avoided.

Cotton socks should be boiled for 10 minutes or soaked for half an hour in a 1:1000 solution of bichloride of mercury before being washed in soap and water.

The bathtub used by a patient with dermatophytosis should be washed with a 1:1000 solution of bichloride or with a dilute solution of cresol, and the bath mat should be used only by the infected person. He should wear paper slippers in walking to and from the bath. To avoid relapses or reinfection the patient should be told to dry his feet most carefully after bathing, paying particular attention to the interspaces between the toes. A dusting powder of 10 per cent sodium thiosulphate in talcum is an excellent preparation to use between the toes and on the soles of the feet daily.

Tinea Manum (Ringworm of the Hands). This fortunately is not a common disease. In the acute inflammatory type of tinea pedis a dermatophytid eruption is common on the sides of the fingers and on the palms. This diagnosis should not be made unless there are active foci of infection on the feet from which mycelia have been recovered. If the diagnosis has been carefully made, a soothing lotion will suffice to dry up these secondary lesions, followed by the following ointment:

Ichthyol		0.66
Calamine		4
Zinc oxide		4
Cold cream	ad	30

rubbed into the affected parts at night.

In the chronic cases caused by the *Trichophyton purpureum*, half strength Whitfield's ointment or 0.1 per cent anthralin ointment will be helpful in eradicating the dry, scaling patches.

Edward A. Oliver

SCABIES

Since the end of the war, with the return of the troops, the incidence of scabies has increased greatly. Not only did many soldiers return with it, but they infected their families on their return. In no other skin disease is the need for cleanliness greater. Previous to the introduction of the newer drugs in the last few years, sulfur was the drug of greatest value. No matter what drug is used the general instructions are the same.

(1) The patient is instructed to take a warm bath, scrubbing vigorously the wrists, the axillae, the hands, and the genitalia, for these are the common locations of the itch mite.

(2) After bathing, the ointment, if it is a sulfur ointment, is thoroughly rubbed into the skin, from the neck to the soles of the feet.

(3) The patient changes the sheets and blankets on his bed, dons clean sleeping garments and clean underclothes the next day.

(4) He anoints himself well every night for 4 nights with this ointment, but does not take a bath until the morning of the fifth day.

(5) After this bath, he changes his underclothes, sheets, and night clothes, and stops treatment.

No treatment is given for a week, but if the itching persists, he repeats the same course.

The formula we commonly use is:

Sulfur precip.		6
Balsam of Peru		6
Sapo viridis		6
Petrolatum	ad	120

This treatment is a valuable and reliable method of treating scabies, but it is messy and dirty, and the average patient does not like it.

In the last few years we have used the drug benzyl benzoate. This is diluted one half for use and the instructions given are the same as are used with the sulfur method of treatment, except that the patient, after taking a bath, applies the solution, then allows it to dry for 10 to 15 minutes, then reapplies it and allows it to remain on his body for 24 hours. He then bathes and changes all his clothes. In many cases one

use is that it is sometimes irritating and produces dermatitis

The latest and what appears to be the best drug for the treatment of scabies is the gamma isomer of hexachlorocyclohexane in a vanishing cream base marketed under the trade name of Kwell Ointment It is white in color and has a faint not unpleasant odor According to a recent report by Cannon and McRae 100 cases were treated with this new ointment with 100 per cent cures The remedy was effective in cases in which other preparations had failed No cases of irritation occurred *either as primary or late manifestation* and no contraindications were elicited even in the presence of severe secondary dermatitis The treatment consists of rubbing into the entire cutaneous surface without preliminary bathing a thin film of cream The patient is requested to refrain from bathing or washing the hands for 24 hours

He is directed to wear clean underwear and night clothes after the bath and to change the bed linen seeing that all are well laundered before re use The patient is then re examined at the end of the week

Edward A Oliver

ERYTHEMA MULTIFORME

Erythema multiforme requires little treatment except to relieve the symptoms of burning and itching A soothing lotion of

Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Liquor calcis	120
Aqua rosae ad	240

dabbed on the affected areas will relieve the burning sensations which often accompany the outbreak of the eruption If joint pains are present sodium salicylate 10 grains (0 6 gm) should be given to relieve them every 3 or 4 hours The bowels should be kept well open and if the patient is running a temperature he should be confined to bed

The treatment should be directed mainly toward *the prevention of a recurrence* For these are common in multiforme erythema A careful examination of the teeth should be made and if abscessed teeth are found they should be extracted Tonsillar tissue that is diseased should likewise be removed *Careful inquiry should be made as to the patient s eating habits* because the disease is at times a manifestation of a food allergy Then too the ingestion of some drugs may be an etiologic factor

When the buccal mucosa is affected and the lips tongue and buccal mucosae are the seat of painful eroded bullae soothing antiseptic mouth washes are of value One of the most useful of these is an iodized phenol mouth wash of

Iodine	2
Phenol	4
Glycerin	6
Alcohol	8
Aqua ad	30

Fifteen drops are diluted in a wineglass of water and used several times a day as a mouth wash

Edward A Oliver

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is a disease characterized by the development of papules vesicles and bullae occurring symmetrically in various sized patches on the limbs sacral region the subscapular areas the antecubital fossae the popliteal spaces and on the legs and arms The eruption is accompanied by severe itching and burning sensations and the disease has the habit of *recurring even after all symptoms* except the pigmentation left in the wake of the eruption have disappeared

For that reason the treatment must be *continuous* The preparation of most value in the past has been arsenic This has been given either as liquor potassii arsenitis Fowler s solution or in the shape of the Asiatic pill which contains arsenous acid and black pepper When Fowler s solution is given dosage begins with 3 minims in water three times a day after meals it is increased 1 drop at each dose until the patient is taking 8 drops t i d pc This is continued until the eruption has involuted then the dose is *decreased until a maintenance dose is found* The Asiatic pill is of three sizes 1/50 1/25 and 1/2 grain The average patient takes 1/25 grain four times daily until the symptoms have

disappeared, then continues on a maintenance dose of 1 or 2 pills a day

The objection to the use of arsenic is that the long continued ingestion of this drug produces arsenical keratoses, which later may become carcinomatous For that reason, the introduction of sulfapyridine in the therapy of dermatitis herpetiformis met with the universal approval of all dermatologists

Sulfapyridine is now the drug found most valuable for the treatment of this annoying disease It is given in 1 gm dosage four times a day, with plenty of water and with sodium bicarbonate, for a week or so until the symptoms have lessened, then the dose is cut down to a maintenance dosage of 1 5 gm a day While the patient is taking sulfapyridine the blood must be carefully examined at frequent intervals and the patient kept under careful observation, because ... drug, and

... g tar and phenol are of value in controlling the pruritus such as the following

Liquor carbonis detergens	6
Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Alcohol	40
Liquor calcis ad	240

An ointment that I have found of value in relieving pruritus is

Sulfur precip	4
Zinc oxide	8
Amyli	16
Oil of cade	8
Menthol	0 33
Acid salicylic	0 33
Ung petrolatum ad	60

The disease is a serious one and the prognosis is not always good Persistence for years, with periods of aggravation and decline, is the rule, though some cases do recover completely

EDWARD A OLIVER

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is an inflammatory dermatosis, in many cases the result of a superimposed infection upon a pre-existing seborrhea It may occur as a scaly, erythematous type of eruption in those areas where the sebaceous glands are most active, i e, the scalp, eyebrows, chest, and pubic region and it may be a moist fissured type which involves the joint flexural surfaces The eruption is characterized by a moderate amount of inflammation, yellowish, greasy scales, and occasional crust formations

Treatment should be directed first to the scalp, regardless of the amount of involvement A valuable lotion is one containing

Euresol pro capillis	6
Hydrarg bichloride	0 18
Spts formicari	30
Spts odorata	30
Spts vini rectif	70
Aqua dest ad	240

This should be thoroughly rubbed into the scalp once a day, using either the tips of the fingers, after carefully parting the hair or a soft cotton pledget, used instead of the tips of the fingers This lotion should be used until all symptoms referable to the scalp have disappeared

If an ointment is preferred, an excellent one is

Sulfur precip	6
Acid salicylic	0 66
Greaseless base ad	60

Numerous greaseless ointment bases are now on the market, and these are much to be preferred to vaseline, lard, or lanolin

An excellent shampoo to be used once a week is resorcin, 10 per cent or euresol 10 per cent in Ph isoderm

If there is weeping and crust formation behind the ears wet compresses of dilute aluminum subacetate solution should be used, followed by a 3 per cent vioform cream

If the retro auricular areas are merely the seat of a scaling fissuring dermatitis, either 3 per cent vioform cream, 3 per cent ammoniated mercury ointment, or an ointment of sulfur precip, 3 per cent and 2 per cent salicylic acid may be used with excellent results For children with moist, exudative areas in the retro auricular regions painting these areas for 2 or 3 days with a 2 per cent aqueous solution of gentian violet is helpful

For seborrheic dermatitis, involving the

nasolabial folds chin and eyebrows a 2 per cent sulfur or ammoniated mercury ointment should be used and for patches elsewhere on the glabrous skin 5 per cent sulfur and 1 per cent salicylic acid in a greaseless base will be found valuable

Sulfur in a paste of 40 per cent strength such as

Sulfur precip	12
Vaseline ad	30

is not nearly so irritating as some of the other weaker sulfur preparations and may often be used advantageously behind the ears on the chest and on the face Before using this however a small area should be tested to see that the skin is not allergic to the ointment

For those areas of weeping flexural seborrheic dermatitis encountered in the axillae cubital fossae groins and popliteal spaces excellent results may be obtained with wet compresses of diluted aluminum subacetate solution or 0 25 per cent silver nitrate solution followed by a 3 per cent vioform cream when the parts are dry 3 per cent ammoniated mercury in zinc oxide ointment may be used

Painting moist eczematous areas with a 2 per cent aqueous solution of gentian violet

discolor and stain underwear and bedclothes

General treatment in all cases should consist of the use of fairly large doses of vitamin B complex and intramuscular injections of crude liver extracts

EDWARD A OLIVER

PSORIASIS

Despite a great deal of investigation little more is known about the etiology of psoriasis than was known 40 years ago The disease may affect the very young or the very old generally it attacks young adults In many cases the lesions will disappear with proper treatment but some cases are most resistant to treatment and the disease invariably tends to recur

The influence of diet is negligible Schamberg found a low protein diet to be of value in some cases I have found that placing large robust individuals on a low fat or fat free diet is sometimes beneficial

In acute cases where the eruption is widespread and superficial internal medication is indicated In this type of case Crocker recommended salicin or sodium salicylate Salicin is given well diluted in water in a dosage of 1 gm three times a day Sodium salicylate is given intravenously twice a week in a dosage of 1 gm

Lecithin in the form of acletin capsules (American Lecithin Co) I have also found of value in acute cases These capsules are given in a dosage of 2 capsules three times daily

Madden employs a fat free diet in most cases and uses vitamin B_1 in a dosage of 1000 units a day many dermatologists give injections of the patient s own blood 10 cc being withdrawn from the median basilic vein and reinjected into the buttocks immediately every other day for a course of 10 to 12 injections

Arsenic should never be used in acute cases and in chronic resistant cases only for a few months at a time It is best administered as Asiatic pills in a dose of 1⁄16 grain (4 mg) four times a day

Topical Treatment In acute rapidly spreading cases local applications should be soothing Calamine liniment bismuth cream (containing bismuth subnitrate—4 zinc oxide—8 liquor calcis—120 and olive oil ad 240) as well as vioform cream (Ciba) 3 per cent are valuable preparations in this type of the disease

As the disease becomes quiescent we commonly use an ointment of ammoniated mercury 3 per cent and 2 per cent salicylic acid in a greaseless base

If the eruption is localized chronic and in patches an excellent ointment is anthralin ointment This should be used in 0 1 per cent strength to begin with and as tolerance is increased its strength can be raised to 0 25 per cent or even 0 5 per cent

Chrysarobin an old favorite may also be used on chronic patches in 3 to 5 per cent strength with 2 to 3 per cent salicylic acid It may be used as an ointment or incorporated in a paint of traumaticin which is a collodion like mixture

Anthralin and chrysarobin ointments are applied to affected areas once a day and

disappeared, then continues on a maintenance dose of 1 or 2 pills a day

The objection to the use of arsenic is that the long continued ingestion of this drug produces arsenical keratoses, which later may become carcinomatous For that reason, the introduction of sulfapyridine in the therapy of dermatitis herpetiformis met with the universal approval of all dermatologists

Sulfapyridine is now the drug found most valuable for the treatment of this annoying disease It is given in 1 gm dosage four times a day, with plenty of water and with sodium bicarbonate, for a week or so until the symptoms have lessened, then the dose is cut down
gm a day
pyridine th
amined at frequent intervals and the patient kept under careful observation because sulfapyridine is not a harmless drug and fatalities have followed its usage

Stimulating lotions containing tar and phenol are of value in controlling the pruritus, such as the following

Liquor carbonis detergens	6
Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Alcohol	40
Liquor calcis ad	240

An ointment that I have found of value in relieving pruritus is

Sulfur precip	4
Zinc oxide	8
Amyli	16
Oil of cade	8
Menthol	0 33
Acid salicylic	0 33
Ung petrolatum ad	60

The disease is a serious one and the prognosis is not always good Persistence for years, with periods of aggravation and decline, is the rule, though some cases do recover completely

Edward A Oliver

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is an inflammatory dermatosis, in many cases the result of a superimposed infection upon a pre existing seborrhea It may occur as a scaly, erythematous type of eruption *in those areas where* the sebaceous glands are most active, i e, the scalp, eyebrows, chest, and pubic region and it may be a moist, fissured type which involves the joint flexural surfaces The eruption is characterized by a moderate amount of inflammation, yellowish greasy scales, and occasional crust formations

Treatment should be directed first to the scalp, regardless of the amount of involvement A valuable lotion is one containing

Euresol pro capillis	6
Hydrarg bichloride	0 18
Spts formicari	30
Spts odorata	30
Spts vini rectif	70
Aqua dest ad	240

This should be thoroughly rubbed into the scalp once a day, using either the tips of the fingers, after carefully parting the hair, *or a soft cotton pledget used instead of the* tips of the fingers This lotion should be used until all symptoms referable to the scalp have disappeared

If an ointment is preferred, an excellent one is

Sulfur precip	6
Acid salicylic	0 66
Greaseless base ad	60

Numerous greaseless ointment bases are now on the market, and these are much to be preferred to vaseline lard or lanolin

An excellent shampoo to be used once a week is resorcin 10 per cent or euresol, 10 per cent in Ph isoderm

If there is weeping and crust formation behind the ears, wet compresses of dilute aluminum subacetate solution should be used, followed by a 3 per cent vioform cream

If the retro auricular areas are merely the seat of a scaling fissuring dermatitis, either 3 per cent vioform cream 3 per cent am*moniated* mercury ointment, or an ointment of sulfur precip, 3 per cent and 2 per cent salicylic acid may be used with excellent results For children with moist, exudative areas in the retro auricular regions painting these areas for 2 or 3 days with a 2 per cent aqueous solution of gentian violet is helpful

For seborrheic dermatitis, involving the

nasolabial folds, chin and eyebrows, a 2 per cent sulfur or ammoniated mercury ointment should be used, and for patches elsewhere on the glabrous skin, 5 per cent sulfur and 1 per cent salicylic acid in a greaseless base, will be found valuable

Sulfur in a paste of 40 per cent strength, such as

Sulfur precip	12
Vaseline ad	30

is not nearly so irritating as some of the other weaker sulfur preparations and may often be used advantageously behind the ears, on the chest, and on the face Before using this, however, a small area should be tested to see that the skin is not allergic to the ointment

For those areas of weeping flexural seborrheic dermatitis encountered in the axillae, cubital fossae, groins, and popliteal spaces excellent results may be obtained with wet compresses of diluted aluminum subacetate solution or 0 25 per cent silver nitrate solution followed by a 3 per cent vioform cream when the parts are dry 3 per cent ammoniated mercury in zinc oxide ointment may be used

Painting moist eczematous areas with a

object to the use of these paints because they discolor and stain underwear and bedclothes

General treatment in all cases should consist of the use of fairly large doses of vitamin B complex and intramuscular injections of crude liver extracts

EDWARD A OLIVER

PSORIASIS

Despite a great deal of investigation, little more is known about the etiology of psoriasis than was known 40 years ago The disease may affect the very young or the very old generally it attacks young adults In many cases the lesions will disappear with proper treatment but some cases are most resistant to treatment and the disease invariably tends to recur

The influence of diet is negligible Schamberg found a low protein diet to be of value in some cases I have found that placing large, robust individuals on a low fat or fat free diet is sometimes beneficial

In acute cases where the eruption is widespread and superficial, internal medication is indicated In this type of case Crocker recommended salicin or sodium salicylate Salicin is given well diluted in water, in a dosage of 1 gm three times a day Sodium salicylate is given intravenously twice a week in a dosage of 1 gm

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If the eruption is localized, chronic and in patches, an excellent ointment is anthralin ointment This should be used in 0 1 per cent strength to begin with, and as tolerance is increased its strength can be raised to 0 25 per cent or even 0 5 per cent

Chrysarobin, an old favorite, may also be used on chronic patches in 3 to 5 per cent strength with 2 to 3 per cent salicylic acid It may be used as an ointment or incorporated in a paint of traumaticin which is a collodion like mixture

Anthralin and chrysarobin ointments are applied to affected areas once a day, and

thoroughly rubbed in After a week or 10 days of this treatment, a zone of erythema appears about the affected patch and the involved area seems irritated Treatment should then be stopped and a soothing cream applied until the irritation has subsided when it may be commenced again Chrysarobin and anthralin should never be used on the face or the scalp and inasmuch as they are both irritating to the eyes the hands should be carefully washed after using them

For generalized cases either subacute or chronic, the Goeckerman treatment with crude coal tar ointment and ultraviolet light is of great value This is practical only in hospitalized patients, it is dirty, but efficient The treatment consists in having the patient anoint himself every night with a crude coal tar ointment of

Crude coal tar	16
Zinc oxide	16
Amyli	120
Petrolatum ad	240

In the morning this is thoroughly removed with olive oil and a good scrub bath with soap and water and the patient then given a generalized lamp treatment, sufficient to produce an erythema These lamp treatments are given three times a week until the eruption has disappeared

Crude coal tar ointment is of value in the topical treatment of psoriasis but in cases where the patient objects to ointments that stain one containing 3 to 6 per cent ammoniated mercury and 2 to 3 per cent salicylic acid is valuable

Psoriasis of the scalp responds best to a greaseless ointment containing 10 per cent ammoniated mercury and 3 per cent salicylic acid Shampooing twice weekly with 10 per cent euresol or resorcin in Ph isoderm is also beneficial Ultraviolet lamp treatments to the scalp are also of value in cases that resist ointment therapy

Roentgen therapy in competent hands is a clean efficient method of clearing up chronic cases that fail to respond to ointments The dose should be 75 r of unfiltered radiation given once a week Treatments should not exceed six or eight It must be remembered that psoriatic skin is easily irritated by roentgen rays and overdosage or too many treatments over a long period of time may lead to radiodermatitis and carcinoma

Ultraviolet lamp therapy, even without the use of coal tar, is often of value in both acute and chronic cases, but treatment should be strong enough to produce an erythema Sun baths are also helpful During the winter months many patients may get relief by basking in the sun in Florida and Arizona The disease is a stubborn one to treat and recurrences are common Much can be accomplished however, by regulating the patient s mode of life and by the judicious use of ointments

EDWARD A OLIVER

PITYRIASIS ROSEA

It is often said that pityriasis rosea is a self limited disease for which no treatment is indicated While in some cases it may disappear with little or no treatment, others may last as long as 6 months Disfigurement from the eruption and pruritus may be quite marked

The course of the disease can be shortened and the pruritus helped by producing mild desquamation of the skin by use of the ultraviolet lamp Three treatments given at intervals of 3 to 5 days, will produce a mild desquamation and generally cure the disease in 2 weeks For the relief of pruritus the following cream is recommended

Bismuth subnitrate	4
Zinc oxide	8
Phenol	2
Liquor calcis	120
Olive oil ad	240

Sulfur, tar, and chrysarobin ointments are not indicated in the treatment of this disease They often will produce a severe dermatitis venenata and prolong the patient s disability

EDWARD A OLIVER

LICHEN PLANUS

The cause of this disease is obscure Numerous clinical observations have confirmed the fact that it frequently occurs in persons who are under nervous strain Many patients are robust, healthy appearing individuals who work and live under tension These

patients should be advised to relax to take life easier get plenty of sleep and to take longer and more frequent vacations Some subjects of the disease are neurotic depressed and in poor health These patients will often be helped by a change of climate and environment

Three drugs mercury, bismuth and arsenic are used in the treatment of lichen planus Mercury is the best It may be given by mouth in the form of the protiodide of

method A 2 per cent solution of bichloride of mercury dissolved in normal salt solution is used and the drug is given in 15 minim dosage deep into the gluteal muscles twice or three times a week This is effective but painful and some patients object to it A preparation less painful is mercury salicylate in oil This may be given in 1 grain dosage twice a week

Another excellent and valuable preparation, which was off the market during the war is mercuric salicyl arsenate called "Enesol" This is not painful and is given in 2 cc dosage intramuscularly twice a week

Bismuth subsalicylate in 2 cc dosage given intramuscularly once a week is not quite so effective as mercury but for patients who do not tolerate injections of mercury it is a valuable substitute It requires from 12 to 15 injections of the bichloride of mercury to clear up the average case of lichen planus and from 8 to 10 injections of bismuth to effect the same result Some cases respond readily to treatment, others are more refractory

Along with intramuscular injections roentgen therapy in competent hands relieves itching and shortens the course of the disease The dosage should be 75 r of unfiltered radiation and this amount may be given to various areas at weekly intervals for five to six treatments with great benefit

For the relief of pruritus until treatment becomes effective the following lotion may be applied to the pruritic areas as often as is necessary

Liquor carbonis detergens	6
Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Magma bentonite ad	240

For the hypertrophic patches that often oc
cı
th
c
every 2 or 3 weeks is of value

If the disease becomes chronic and there are residues which fail to respond to ordinary treatment arsenic is often beneficial It is best given as the Asiatic pill in 1/16 grain (4 mg) dosage t i d p c

Lichen planus of the mucous membranes is difficult to cure In many instances patches of lichen planus on the buccal mucosa or on the tongue will remain long after the cutaneous manifestations have disappeared Vitamin B complex either by mouth or by injection has been recommended by Burgess of Montreal who reported success in treatment of this condition in a limited number of cases I have found this form of the disease difficult to cure

EDWARD A OLIVER

ECZEMATOID DERMATITIS

Atopic Eczema This type of eczema occurs in the infant in the child the adolescent and in the adult It is intimately associated with the atopic forms of sensitivity and there is a close association between this form of eczema and asthma hay fever and migraine In many cases of infantile and childhood eczema a clear cut family history of one of these diseases is obtainable on careful questioning of the parents

INFANTILE ECZEMA The baby s diet should be carefully investigated Many of these children are bottlefed on cow s milk Substituting goat s milk soybean preparations boiled milk or evaporated milk for cow s milk will often prove of value Orange juice and cod liver oil should also be avoided for several months

Soap should never be used on the eczematous skin In its place one may use one of the many detergents now on the market or olive oil Colloid baths however containing soda and starch may be tried The child should be kept in a cool room and the clothing should be light soft and cool Con

tact with wool, silk, and rayon should be avoided and only cotton garments worn

House dust and the substances emanating from mattresses, pillows, bedding, and rugs are often allergenic factors, so they should be avoided as much as possible

The child should be prevented from mutilating his skin by the wearing of cardboard splints in the bend of his elbows, by pinning down the arms of his night clothes to the bedding at night, and by having him wear a soft muslin mask

For topical therapy some form of coal tar affords more relief than anything else Coal tar should not be used if the child is exposed to strong wind or sunlight shortly after its use because coal tar renders the skin quite photosensitive

Crude coal tar ointment containing

Crude coal tar	2
Zinc oxide	2
Amyli	15
Vaseline	15

may be used in full strength, or it may be diluted with equal parts of vaseline or zinc oxide ointment

Davalan pediatric ointment (Dow Chemical Co) is an excellent tar ointment If the baby's skin does not tolerate tar well, an ointment of

Naphthalan	3
Ichthyol	0 66
Zinc oxide	8
Amyli	7
Vaseline ad	30

may be used in its place Ammoniated mercury ointment is often irritating to the eczematous skin and should not be used

Atopic Eczema in Older Children and Young Adults Treatment includes three different approaches

Local Treatment Pruritus must be alleviated or the patients will scratch and mutilate their skin Topical remedies, such as crude coal tar ointment, ointments containing phenol in 0 5 per cent or 1 per cent, menthol 0 25 per cent to 0 5 per cent, liquor carbonis detergens and aluminum subacetate solution may be used

Two new antihistamine ointments that will often relieve pruritus and help the eczema are theophorin ointment (Hoffmann LaRoche, and pyribenzamine cream (Ciba)

Soapless detergents, of which there are many on the market, should be used instead of soap Soap is not tolerated well by the eczematous skin

Elimination Treatment All offending irritants should be eliminated as far as possible These are dust, wool, silk rayon cat hair, and feathers A simple diet should be prescribed, and foods such as eggs fish, pork, nuts, cheese, tomatoes, and chocolate should be avoided

If foci of infection such as diseased tonsils or abscessed teeth are present, they should be removed

Sedation Sedative drugs, such as small doses of phenobarbital, are often indicated in atopic eczema, as these patients are nervous, overactive individuals The antihistamine drugs, pyribenzamine, hydryllin, benadryl and theophorin should all be tried In some cases I have found them helpful, in others disappointing

The physician attending these unfortunate individuals should make every effort to understand them Many of them have problems which they hesitate to talk about Clearing up these problems may help the disease because here, as in no other disease, is there a psychosomatic background Many of these patients need psychiatric care, and in many cases a complete change of scene and life in another climate are of more benefit than anything else

Nummular Eczema Nummular eczema occurs in coin sized patches and affects primarily the dorsal surfaces of the hands and forearms and the extensor aspect of the legs and thighs It is always worse in winter and generally clears in the summer, but has a tendency to recur frequently Exposure to soap and water, acids and alkalies, as well as oils and grease, favors its development

It is commonly seen in housewives, dishwashers, and surgeons, and the foci of infection in the teeth, tonsils, and prostate may be predisposing factors in its development

The disease is a stubborn one to treat If the patient is anemic and physically below par, suitable tonics should be prescribed Foci of infection should be removed and since many cases improve in the summer, the patient may be helped by generalized ex

posures to ultraviolet light and with liberal sized doses of vitamins A and D A change of climate is also beneficial to some Mild antiparasitic treatment seems to help this type of eczema more than antieczematous treatment Painting the lesions with 5 per cent crude coal tar in chloroform is of value

Vioform ointment 3 per cent (Ciba) is also helpful, and painting individual patches with a 3 to 5 per cent solution of silver nitrate every 3 or 4 days, is useful

When the lesions are dry, the use of crude coal tar ointment is of definite value

Eczematous Contact Dermatitis Eczematous contact dermatitis, or dermatitis venenata, is an inflammation of the skin due to occasional, continuous or intermittent contact with a cutaneous irritant Among the common causes of contact dermatitis are

(1) *Plants,* such as primroses chrysanthemums, the Rhus family of ivy oak and sumac, ragweed, geranium, and tomato plants

(2) *Drugs* Alkalies, soaps soda butyn cocaine, novocain, iodoform picric acid, and resorcin

(3) *Miscellaneous Irritants* Hair dyes clothing dyes, depilatories, nail polishes cosmetics, adhesive plaster, and dress shields

The dermatitis may be acute or chronic If acute it is characterized by redness edema and the formation of papules and vesicles If chronic it is characterized by scales crusts and infiltration of the skin

The first essential of treatment is to remove the cause, if this can be discovered Careful history taking will often give a definite clue as to what has produced the dermatitis

When the involved parts are acutely inflamed, wet dressings are indicated One of the best preparations to use on an inflamed skin is aluminum subacetate solution, diluted 1 oz to 1 pint of cool water or cool milk and applied in the form of wet compresses

Dilute solutions of subacetate of lead are also of value, and if infection is superimposed on an inflamed skin wet dressings of silver nitrate, aqueous solutions of 1/4th to 1/8th strength are beneficial Compresses of a 1 4000 solution of potassium permanganate are also of value in a pustular dermatitis

As the inflammation subsides lotions or ointments may be used The familiar calamine lotion or the following lotion may be used with benefit

Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Liquor calcis	120
Magma bentonite ad	240

When the parts are dry, the following ointments will prove helpful in curing the dermatitis

(1)	Ichthyol	66
	Calamine	4
	Zinc oxide	4
	Ung aqua rosae ad	30
(2)	Naphthalan	3
	Ichthyol	0 66
	Zinc oxide	8
	Amyli	7
	Vaseline ad	30
(3)	Crude coal tar	2
	Zinc oxide	2
	Amyli	15
	Vaseline ad	30

and Lassar s paste

EDWARD A OLIVER

TINEA VERSICOLOR

This is a common superficial fungous infection and is often present for months before the patient seeks treatment The disease is marked by fawn colored patches of various sizes, most often seen on the chest and anterior trunk

The treatment is simple The patient is instructed to scrub the affected parts at night with soap and water While the skin is still moist, a solution of vinegar is dabbed on the affected areas, and while this is still [illegible] per [illegible] ation [illegible] with the sodium hyposulfite solution produces nascent sulfurous acid which rapidly kills the fungus and cures the disease in a week to 10 days

A half strength Whitfield s ointment, such as

Acid salicylic	1
Acid benzoic	2
Ung petrolatum	15
Ung aqua rosae	15

will also clear up the condition rapidly if applied to the affected areas for about a week

EDWARD A OLIVER

PRURITUS ANI

This somewhat common condition is often seen in high strung, nervous, and tense individuals It may, however, occur in normal, well balanced, and even phlegmatic persons

There are many causes besides nervous tension Fungous infection may be present, the patient may be allergic to toilet paper or toilet soap, he may have a pinworm infection of the bowel or he may suffer from hemorrhoids, fissures, and polyps Liver disease also may be a factor in the production of anal pruritus

In every case a complete history should be taken and a careful examination made If the patient has a fungous infection (tinea cruris) in the groin or between the toes, that infection should receive treatment Hemorrhoids, fissures, and polyps should be excised

Many patients respond to simple combined treatment, which includes the use of roentgen rays, topical remedies, sedation and diet

The diet should be bland Spices, alcohol, and foods containing small seeds should be avoided Coffee should be limited to 1 or 2 cups daily, and the use of tobacco should be curtailed

The patient should never use soap on the affected parts The too energetic use of soap in taking a shower bath often starts pruritus ani Considerable relief may be had by taking a hot sitz bath, medicated or unmedicated For these sitz baths camomile tea and potassium permanganate are among the better antipruritic agents If camomile tea is used, an infusion should be brewed and from 10 to 25 cc used in a tub of water In using potassium permanganate, dissolve 1 teaspoonful or 1 tablespoonful of crystals in a quart of water, and use 1 quart to a tub of water Care should be taken to see that the crystals are completely dissolved otherwise contact with the skin produces a burn

The patient should cleanse the parts immediately after defecation with a warm wet wash cloth or with moist absorbent cotton Toilet paper should not be used It is also a good procedure to have the patient apply zinc oxide ointment to the anal area before defecation, removing it immediately afterward with olive oil, and then using the prescribed medication

For topical remedies some patients prefer lotions, others prefer ointments If lotions are used, I often prescribe the following one keeping a pledget of cotton saturated with it in the anal crease for a week or so until the patient gets relief

Zinc oxide	12
Talcum	8
Glycerin	6
Phenol	2
Liquor calcis	120
Magma bentonite q s ad	240

To this may be added liquor carbonis detergens 6 to 12 gm

If the parts are moist and macerated, a monilia infection may be present, then painting with a 2 per cent solution of gentian violet or a 0 5 to 1 per cent solution of brilliant green will be effective

If there is considerable inflammation and eczematous reaction present, wet compresses of aluminum subacetate solution, diluted 1 ounce to 1 pint of cool water, or silver nitrate solution diluted 2 teaspoonfuls of a 10 per cent solution to 1 pint of cool water, are indicated

If a fungous infection is present, either of the following ointments or the lotion, will prove effective

Sulfur precip	1
Acid salicylic	1
Cold cream	15
Vaseline	15
or	
Acid salicylic	0 66
Acid benzoic	1 2
Cold cream	15
Vaseline	15

or

Resorcin	12
Calamine lotion ad	240

In uncomplicated cases good results will often be obtained with mercury A good ointment to use is

Hydrarg ammoniatum	1
Ung zinc oxide ad	30
or	
Pulv calomel	4
Boric acid	4
Menthol	0 15
Cold cream ad	30

The new antihistamine ointments, theophorin ointment (Hoffmann LaRoche) or pyribenzamine cream (Ciba) often give prompt relief

Coal tar ointments, such as

Daxalan ointment	15
Ung zinc oxide	15
or	
Crude coal tar	2
Zinc oxide	2
Amyli	15
Vaseline	15

are also valuable

The patient may require sedation, and in that case phenobarbital in dosage of ¼ to ½ grain (15 to 30 mg) may be given three or four times daily

The antihistamine drugs, hydryllin, pyribenzamine, or benadryl, are often of considerable value in relieving pruritus, as is acid acetylsalicylic in 5 grain (0 3 gm) doses, three or four times daily

Roentgen therapy is one of the best remedies we have for the control and even cure of this annoying condition In competent hands, roentgen therapy will do more to give the patient complete relief than almost any other remedy A dose of 75 r is given to the affected area once a week for from four to six treatments In most cases this amount will alleviate most of the pruritus, and treatment should be stopped If there is a recurrence, four more such treatments of 75 r unfiltered may be given It is not safe to give more than this amount Radiodermatitis and other unfortunate sequelae may occur

Finally if all these measures fail injection of alcohol by a competent surgeon may effect a cure

EDWARD A OLIVER

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